Day : Monday
Date: 9/18/2006
Time: 14:08:56

PALM INTRANET

Inventor Information for 10/727655

Inventor Name	City	State/Country
SZELENYI, ISTVAN	SCHWAIG	GERMANY
BRUNE, KAY	MARLOFFSTEIN	GERMANY
HERMANN, ROBERT	HANAU	GERMANY
LOCHER, MATHIAS	RONNEBURG	GERMANY

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity/Reexam | Foreign Data | Invento

Search Another: Application# [ ] Search **or Patent#** [ ] Search

PCT / [ ] / [ ] Search **or PG PUBS #** [ ] Search

Attorney Docket # [ ] Search

Bar Code # [ ] Search

To go back use Back button on your browser toolbar.

Back to PALM | ASSIGNMENT | OASIS | Home page

Sodium ion channel

From Wikipedia, the free encyclopedia

Sodium channels (also known as "voltage-gated **sodium** channels") are integral membrane proteins that are localized in and conduct **sodium** ions (Na^+) through a cell's plasma membrane. Many of the ionotropic receptors are also able to conduct **sodium** ions and are discussed elsewhere. In excitable cells such as neurons and myocytes, **sodium** channels are responsible for the rising phase of action potentials.

Contents

Structure

Sodium channels can often be isolated from cells as a complex of two types of protein subunits, α and β. An α subunit forms the core of the **channel**. When the α subunit protein is expressed by a cell, it is able to form channels which conduct Na^+ in a voltage-gated way, even if β subunits are not expressed. When β subunits assemble with α subunits the resulting complex can display altered voltage dependence and cellular localization.

The α-subunit has four repeat domains, labeled I through IV, each containing six membrane-spanning regions, labeled S1 through S6. The highly conserved S4 region acts as the **channel's** voltage sensor. The voltage sensitivity of this **channel** is due to positive amino acids located at every third position. When stimulated by a change in transmembrane voltage, this region moves toward the extracellular side of the cell membrane, allowing the **channel** to become permeable to ions. The ions are conducted through a pore, which can be broken into two regions. The more external (i.e., more extracellular) portion of the pore is formed by the "P-loops" (the region between S5 and S6) of the four domains. This region is the most narrow part of the pore and is responsible for its ion selectivity. The inner portion (i.e., more cytoplasmic) of the pore is formed by the combined S5 and S6 regions of the four domains. The region linking domains III and IV is also important for **channel** function. This region plugs the **channel** after prolonged activation, inactivating it.

Gating

Voltage-gated **sodium** channels can have three types of states: deactivated (closed), activated (open), and inactivated (closed).

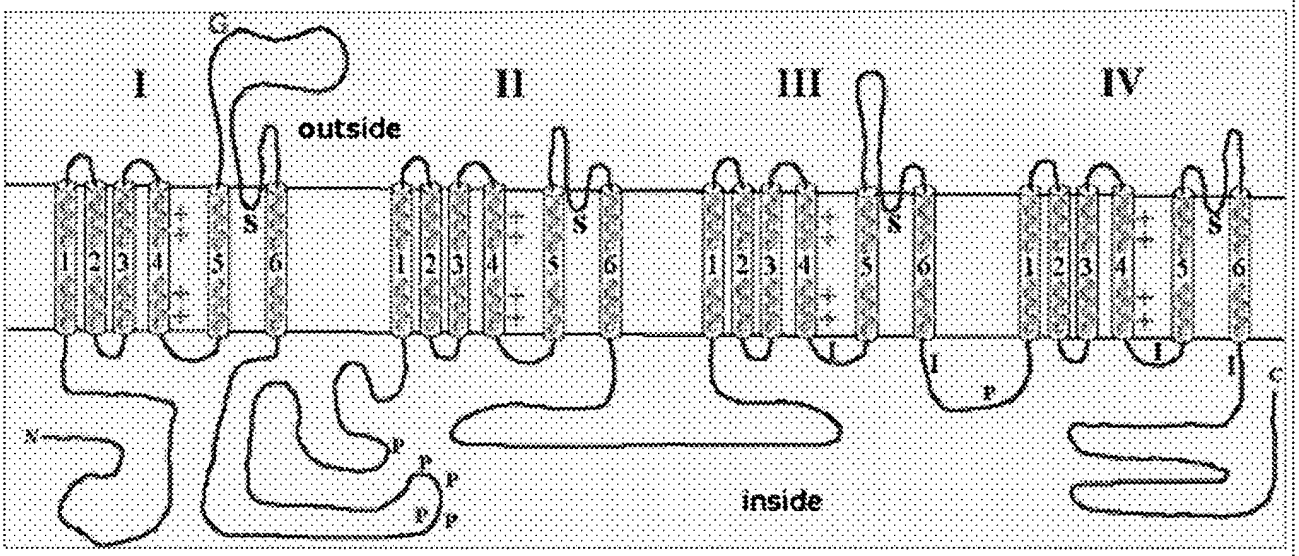


Diagram of a voltage-sensitive **sodium channel** α-subunit. G - glycosylation, P - phosphorylation, S - ion selectivity, I - inactivation, positive (+) charges in S4 are important for transmembrane voltage sensing[1].

Channels in the deactivated state are thought to be blocked on their intracellular side by an "activation gate", which is removed in response to stimulation that opens the **channel**. The ability to inactivate is thought to be due to a tethered plug (formed by domains III and IV of the alpha subunit), called an inactivation gate, that blocks the inside of the **channel** shortly after it has been activated. During an action potential the **channel** remains inactivated for a few milliseconds after depolarization. The inactivation is removed when the membrane potential of the cell repolarizes following the falling phase of the action potential. This allows the channels to be activated again during the next action potential. Genetic diseases that alter Na^+ **channel** inactivation cause muscle stiffness because of the introduction of a window current.

The temporal behaviour of **sodium** channels can be described by a Markovian scheme or by the Hodgkin-Huxley-type formalism. In the former scheme, each **channel** occupies a distinct state out of several with differential equations describing transitions between states; in the latter, the channels are treated as a population that are affected by three independent gating variables. Each of these variables can attain a value between 1 (fully permeant to ions) and 0 (fully non-permeant), the product of these variables yielding the percentage of conducting channels.

Impermeability to other ions

The pore of **sodium** channels contains a selectivity filter made of negatively charged amino acid residues, which attract the positive Na^+ ion and keep out negatively charged ions such as chloride. The cations flow into a more constricted part of the pore that is 0.3 by 0.5 nm wide, which is just large enough to allow a single Na^+ ion with a water molecule associated to pass through. The larger K^+ ion cannot fit through this area. Differently sized ions also cannot interact as well with the negatively charged glutamic acid residues that line the pore.

Diversity

The family of **sodium** channels has nine known members, with amino acid identity >50% in the transmembrane and extracellular loop regions. A standardized nomenclature for **sodium** channels is currently used and is maintain by the IUPHAR.[2] The proteins of these channels are named $Na_v1.1$ through $Na_v1.9$. The gene names are referred to as SCN1A through SCN11A (the SCN6/7A gene is part of the Na_x sub-family and has uncertain function). The likely evolutionary relationship between these channels, based on the similarity of their amino acid sequences, is shown in figure 1. The individual **sodium** channels are distinguished not only by differences in their sequence but also by their kinetics and expression profiles. Some of this data is summarized in table 1, below.

Table 1. Nomenclature and some function of voltage-gated sodium channels

Protein	Gene	Auxiliary	Expression profile	Associated human channelopathies

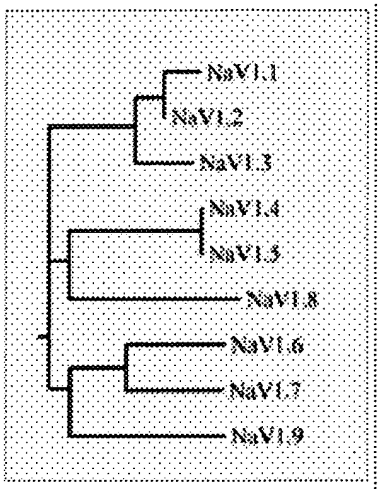


Figure 1. Likely evolutionary relationship of the nine known human **sodium** channels.

name	name	subunits		
$Na_v1.1$	SCN1A	β1,β2,β3,β4	Central neurons and cardiac myocytes	Inherited febrile epilepsy, GEFS and myoclonic epilepsy
$Na_v1.2$	SCN2A	β1,β2,β3,β4	Central neurons	inherited febrile seizures and epilepsy
$Na_v1.3$	SCN3A	β1,β3	Central neurons and cardiac myocytes	none known
$Na_v1.4$	SCN4A	β1	Skeletal muscle	hyperkalemic periodic paralysis, Paramyotonia congenita, and potassium-aggravated myotonia
$Na_v1.5$	SCN5A	β1,β2,β3,β4	Central neurons	Long QT Syndrome, Brugada syndrome, and idiopathic ventricular fibrillation
$Na_v1.6$	SCN8A	β1,β2	Central neurons, dorsal root ganglia, peripheral neurons	none known
$Na_v1.7$	SCN9A	β1,β2	Dorsal root ganglia, sympathetic neurons, Schwann cells, and neuroendocrine cells	inherited erythromelalgia
$Na_v1.8$	SCN10A	unknown	Dorsal root ganglia	none known
$Na_v1.9$	SCN11A	unknown	Dorsal root ganglia	none known

Role in action potential

Voltage-gated ion **channel sodium** channels play a significant role in action potentials. If enough channels open when there is a change in the cell's membrane potential, a large number of Na^+ ions will rush into the cell down their electrochemical gradient, further depolarizing the cell. Thus, the more Na^+ channels localized in a region of a cell's membrane, the faster the action potential will propagate, and the more excitable that area of the cell will be. Na^+ channels both open and close more quickly than K^+ channels, producing an influx of positive charge (Na^+) toward the beginning of the action potential and an efflux (K^+) toward the end.

References

1. ^ Frank H. Yu and William A. Catterall (2003) "Overview of the voltage-gated **sodium channel** family" in *Genome Biol.* 4(3): 207. (Full text online (http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=153452))
2. ^ http://iuphar.org

- Eric R. Kandel, Schwartz JH, Jessell TM. *Principles of Neural Science*, 4th ed., pp.154-169. McGraw-Hill, New York (2000). ISBN 0-8385-7701-6
- Bertil Hille *Ion channels of excitable membranes*, 3rd ed., Sinauer Associates, Sunderland, MA (2001). ISBN 0-87893-321-2
- Catterall, WA, Goldin, AL, and Waxman, SG. (2005), International Union of Pharmacology. XLVII. Nomenclature and Structure-Function Relationships of Voltage-Gated **Sodium** Channels. *Pharmacol. Rev.* 57, 397-409. Entrez PubMed 16382098 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16382098)

See also

- Ion channels
- Calcium channels
- Potassium channels
- Resting ion channels

Retrieved from "http://en.wikipedia.org/wiki/Sodium_ion_channel"

Categories: Proteins | Ion channels | **Sodium**

Ion channel

From Wikipedia, the free encyclopedia

Ion channels are pore-forming proteins that help to establish and control the small voltage gradient that exists across the plasma membrane of all living cells (see cell potential) by allowing the flow of ions down their electrochemical gradient. They are present in the membranes that surround all biological cells.

Contents

Basic features

An ion **channel** is an integral membrane protein or more typically an assembly of several proteins. Such "multi-subunit" assemblies usually involve a circular arrangement of identical or homologous proteins closely packed around a water-filled pore through the plane of the membrane or lipid bilayer.[1] The pore-forming subunit(s) are called the α subunit, while the auxiliary subunits are denoted β, γ, and so on. While some channels permit the passage of ions based solely on charge, the archetypal **channel** pore is just one or two atoms wide at its narrowest point. It conducts a specific species of ion, such as **sodium** or **potassium**, and conveys them through the membrane single file--nearly as quickly as the ions move through free fluid. In some ion channels, passage through the pore is governed by a "gate," which may be opened or closed by chemical or electrical signals, temperature, or mechanical force, depending on the variety of **channel**.

Biological role

Because "voltage-gated" channels underlie the nerve impulse and because "transmitter-gated" channels mediate conduction across the synapses, channels are especially prominent components of the nervous system. Indeed, most of the offensive and defensive toxins that organisms have evolved for shutting down the nervous systems of predators and prey (e.g., the venoms produced by spiders, scorpions, snakes, fish, bees, sea snails and others) work by plugging ion **channel** pores. In addition, ion channels figure in a wide variety of biological processes that involve rapid changes in cells, such as cardiac, skeletal, and smooth muscle contraction, epithelial transport of nutrients and ions, T-cell activation and pancreatic beta-cell insulin release. In the search for

new drugs, ion channels are a favorite target.

Diversity

- Voltage-gated **sodium** channels: Like other voltage-gated channels, these channels open and close in response to membrane potential. This family contains at least 9 members and is largely responsible for action potential creation and propagation. The pore-forming α subunits are very large (up to 4,000 amino acids) and consist of four homologous repeat domains (I-IV) each comprising six transmembrane segments (S1-S6) for a total of 24 transmembrane segments. The members of this family also coassemble with auxiliary β subunits, each spanning the membrane once. Both α and β subunits are extensively glycosylated.

- Voltage-gated calcium channels: As with the other voltage-gated channels, these open and close according to the membrane potential. This family contains 10 members, though these members are known to coassemble with $\alpha_2\delta$, β, and γ subunits. These channels play an important role in both linking muscle excitation with contraction as well as neuronal excitation with transmitter release. The α subunits have an overall structural resemblance to those of the **sodium** channels and are equally large.

- **Potassium** channels: This superfamily is comprised of four families of channels, which are grouped based on homology and activation. **Potassium** channels are near ubiquitous in their expression and are primarily permeable to **potassium** over other ions.

  - Voltage-gated **potassium** channels: Like other voltage-gated channels, these K_V channels open and close according to membrane potential. This family contains almost 40 members, which are further divided into 12 subfamilies. These channels are known mainly for their role in repolarizing the cell membrane following action potentials. The α subunits have six transmembrane segments, homologous to a single domain of the **sodium** channels. Correspondingly, they assemble as tetramers to produce a functioning **channel**.
  - Calcium-activated **potassium** channels: This family of channels is, for the most part, activated by intracellular Ca^{2+} and contains 8 members. It should be noted, however, that some of these channels (the $K_{Ca}4$ and $K_{Ca}5$ channels) are responsive instead to intracellular Na^+ and Cl^-. Furthermore, the $K_{Ca}1$ family is both Ca^{2+} and voltage activated, further complicating the description of this family. The K_{Ca} **channel** α subunits have six transmembrane segments similar to the K_Vs, except $K_{Ca}1$, in which the N-terminus makes a seventh pass across the membrane to end up outside the cell. The α subunits make homo- and hetero-tetrameric complexes.
  - Inward-rectifier **potassium** channels: These channels allow **potassium** to flow into the cell in an inwardly rectifying manner, i.e, **potassium** flows effectively into, but not out of, the cell. This family is composed of 15 official and 1 unofficial members and is further subdivided into 7 subfamilies based on homology. These channels are affected by intracellular ATP, PIP_2, and G-protein βγ subunits. They are involved in important physiological processes such as the pacemaker activity in the heart, insulin release, and **potassium** uptake in glial cells. They contain only two transmembrane segments, corresponding to the core pore-forming segments of the K_V and K_{Ca} channels. Their α subunits form tetramers.
  - Two-pore-domain **potassium** channels: This family of 15 members form what is known as leak channels, and they follow Goldman-Hodgkin-Katz (open) rectification. These channels are regulated by numerous mechanisms, including: oxygen tension, pH, mechanical stretch, and G-proteins. Their name is derived from the fact that the α subunits consist of four transmembrane segments, each containing two pore loops. As such, they structurally correspond to two inward-rectifier α subunits and thus form dimers in the membrane.

- Chloride channels: This superfamily of poorly understood channels consists of approximately 13 members. Chloride channels are important for setting cell resting membrane potential and maintaining proper cell volume. These channels conduct Cl^- as well as other anions such as HCO_3^-, I^-, SCN^-, and NO_3^-. The structure of these channels is also not other known channels. Chloride **channel** subunits contain between 1 and 12 transmembrane segments. Some members of this family are activated by voltage, while others are activated by Ca^{2+}, extracellular ligands, and pH among other modulators. [2]

- Transient receptor potential channels: This group of channels, normally referred to simply as TRP channels, is named after their role in Drosophila phototransduction. This family, containing at least 28 members, is incredibly diverse in its method

of activation. Some TRP channels seem to be constitutively open, while others are gated by voltage, intracellular Ca^{2+}, pH, redox state, osmolarity, and mechanical stretch. These channels also vary according to the ion(s) they pass, some being selective for Ca^{2+} while others are less selective, acting as cation channels. This family is subdivided into 6 subfamilies based on homology: classical (TRPC), vanilloid receptors (TRPV), melastatin (TRPM), polycystins (TRPP), mucolipins (TRPML), and ankyrin transmembrane protein 1 (TRPA).

- Cyclic nucleotide-gated channels: This superfamily of channels contains two families: the cyclic nucleotide-gated (CNG) channels and the hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels.
    - Cyclic nucleotide-gated channels: This family of channels is characterized by activation due to the binding of intracellular cAMP or cGMP, with specificity varying by member. These channels are primarily permeable to monovalent cations such as K^+ and Na^+. They are also permeable to Ca^{2+}, though it acts to close them. There are 6 members of this family, which is divided into 2 subfamilies.
    - Hyperpolarization-activated, cyclic nucleotide-gated channels: While these channels are voltage-gated, their opening is due to hyperpolarization rather than the depolarization required for other like channels. These channels are also sensitive to the cyclic nucleotides cAMP and cGMP, which alter the voltage sensitivity of the **channel**'s opening. These channels are permeable to the monovalent cations K^+ and Na^+. There are 4 members of this family, all of which form tetramers of six-transmembrane α subunits. As these channels open under hyperpolarizing conditions, they function as pacemaking channels in the heart, particularly the SA node.
- Cation channels of sperm: This small family of channels, normally referred to as Catsper channels, is related to the two-pore channels and distantly related to TRP channels. The 4 members of this family form voltage-gated Ca^{2+} channels that seem to be specific to sperm. These channels are required form proper fertilization. The study of these channels has been slow because they do not traffick to the cell membrane in many heterologous systems.
- Two-pore channels: This small family of 2 members putatively forms cation-selective ion channels. They are predicted to contain two K_V-style six-transmembrane domains, suggesting they form a dimer in the membrane. These channels are related to catsper channels channels and, more distantly, TRP channels.
- Light-gated channels like channelrhodopsin are directly opened by the action of light.
- *Ligand-gated* channels (LGICs): Also known as ionotropic receptors, this group of channels open in response to specific ligand molecules binding to the extracellular domain of the receptor protein. Ligand binding causes a conformational change in the structure of the **channel** protein that ultimately leads to the opening of the **channel** gate and subsequent ion flux across the plasma membrane. Examples of LGICs include the cation-permeable "nicotinic" Acetylcholine receptor, ionotropic glutamate-gated receptors and ATP-gated P2X receptors, and the anion-permeable γ-aminobutyric acid-gated $GABA_A$ receptor.

Detailed structure

Channels differ with respect to the ion they let pass (for example, Na^+, K^+, Cl^-), the ways in which they may be regulated, the number of subunits of which they are composed and other aspects of structure. Channels belonging to the largest class, which includes the voltage-gated channels that underlie the nerve impulse, consists of four subunits with six transmembrane helices each. On activation, these helices move about and open the pore. Two of these six helices are separated by a loop that lines the pore and is the primary determinant of ion selectivity and conductance in this **channel** class and some others. The existence and mechanism for ion selectivity was first postulated in the 1960s by Clay Armstrong. The **channel** subunits of one such other class, for example, consist of just this "P" loop and two transmembrane helices. The determination of their molecular structure by Roderick MacKinnon using X-ray crystallography won a share of the 2003 Nobel Prize in Chemistry.

Because of their small size and the difficulty of crystallizing integral membrane proteins for X-ray analysis, it is only very recently that scientists have been able to directly examine what channels "look like." Particularly in cases where the crystallography required removing channels from their membranes with detergent, many researchers regard images that have been obtained as tentative. An example is the long-awaited crystal structure of a voltage-gated **potassium channel**, which was reported in May 2003. One inevitable ambiguity about these structures relates to the strong evidence that channels change conformation as they

operate (they open and close, for example), such that the structure in the crystal could represent any one of these operational states. Most of what researchers have deduced about **channel** operation so far they have established through electrophysiology, biochemistry, gene sequence comparison and mutagenesis.

Diseases of Ion Channels

There are a number of chemicals and genetic disorders which disrupt normal functioning of ion channels and have disastrous consequences for the organism. Genetic disorders of ion channels and their modifiers are known as Channelopathies. See Category:Channelopathy for a full list.

Chemicals

- Tetrodotoxin (TTX), used by puffer fish and some types of newts for defense. It is a **sodium channel** blocker.
- Saxitoxin, produced by a dinoflagellate also known as red tide. It blocks voltage dependent **sodium** channels.
- Conotoxin, which is used by cone snails to hunt prey.
- Lidocaine and Novocaine belong to a class of local anesthetics which block **sodium** ion channels.
- Dendrotoxin is produced by mamba snakes which blocks **potassium** channels.

Genetic

- Shaker gene mutations cause a defect in the volatage gated ion channels, slowing down the repolarization of the cell.
- Equine hyperkalaemic periodic paralysis as well as Human hyperkalaemic periodic paralysis (HyperPP) are caused by a defect in voltage dependent **sodium** channels.
- Paramyotonia congenital (PC) and **potassium** aggravated myotonias (PAM)
- Generalized epilepsy with febrile seizures (GEFS)
- Episodic Ataxia Type-1 (EA1)
- Familial hemiplegic migraine (FHM)
- spinocerebellar ataxia type 13

History

The existence of ion channels was hypothesized by the British biophysicists Alan Hodgkin and Andrew Huxley as part of their Nobel Prize-winning theory of the nerve impulse, published in 1952. The existence of ion channels was confirmed in the 1970s with an electrical recording technique known as the "patch clamp," which led to a Nobel Prize to Erwin Neher and Bert Sakmann, the technique's inventors. Hundreds if not thousands of researchers continue to pursue a more detailed understanding of how these proteins work. In recent years the development of automated patch clamp devices helped to increase the throughput in ion **channel** screening significantly.

The Nobel Prize in chemistry for 2003 was awarded to two American scientist; to Roderick MacKinnon for his studies on the physico-chemical properties of ion **channel** function, including x-ray crystallographic structure studies; and to Peter Agre for his similar work on aquaporins.

Reference:

- Nobel Prize Press Release (http://nobelprize.org/nobel_prizes/chemistry/laureates/2003/press.html)

References

1. ^ Two textbooks that discuss ion channels are: *Neuroscience* (2nd edition) Dale Purves, George J. Augustine, David Fitzpatrick, Lawrence. C. Katz, Anthony-Samuel LaMantia, James O. McNamara, S. Mark Williams, editors. Published by Sinauer Associates, Inc. (2001) online textbook (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=neurosci.chapter.227) and *Basic Neurochemistry: Molecular, Cellular, and Medical Aspects* (6th edition) by George J Siegel, Bernard W Agranoff, R. W Albers, Stephen K Fisher and Michael D Uhler published by Lippincott, Williams & Wilkins (1999): online textbook (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=bnchm.chapter.421)

2. ^ Suzuki M., Morita T. and Iwamoto, T. (2006) Diversity of Cl(-) channels. *Cell Mol Life Sci.* 63(1):12-24. Entrez PubMed 16314923 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16314923)

- Bertil Hille *Ion channels of excitable membranes*, 3rd ed., Sinauer Associates, Sunderland, MA (2001). ISBN 0-87893-321-2
- International Union of Pharmacologists, Ion **channel** compendium (http://www.iuphar-db.org/iuphar-ic/index.html)

See also

- action potential
- active transport
- channelopathy
- neurotoxin
- passive transport
- transmembrane receptor

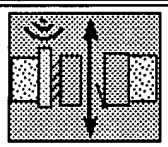
External links

- The Voltage Sensor in Voltage-Dependent Ion Channels (http://physrev.physiology.org/cgi/content/full/80/2/555)
- X-ray crystal structure of a **potassium channel**
- Recent literature and ion **channel** lab registry
- Neuromuscular Disease Center at Washington University
- Calcium Channels (Animation)

Retrieved from "http://en.wikipedia.org/wiki/Ion_channel"

Categories: Biochemistry | Neuroscience | Ion channels

ION CHANNELS, TRANSMITTERS, RECEPTORS & DISEASE



CHANNEL TYPES: General[9]

- **Extracellular ligand-gated channels**: Nicotinoid
  - 5 Homologous polypeptide subunits
  - Subunits have 4 membrane spanning regions
  - Ligands: Neurotransmitters
  - Specific receptors
    - Nicotinic AChR
    - $GABA_A$ & $GABA_C$
    - Glycine
    - 5-HT3
    - Glutamate activated anionic channels
      - Types: NMDA; AMPA; Kainate
      - 4 Homologous subunits
- **Intracellular ligand-gated channels**
  - Ligands: cAMP, cGMP, Ca^{++}, G-proteins, Phosphorylation
- **Voltage-gated channels**
  - 4 domains
    - Na^+ & Ca^+ channels: In single polypeptide chain
    - K^+ **channel**: Tetramer of 4 similar subunits
  - Each domain has 6 membrane spanning regions
  - S4 sequence
    - Contains + charged amino acids (lysine and/or arginine)
    - "Senses" voltage across membrane: Regulates pore opening
  - Selective **channel** pore (Bacterial K^+ **channel** model)
    - Dimensions: 12 Å long; 3 Å wide
    - Lined by main chain oxygen atoms
  - Ion selectivity: Na^+, Ca^{++} or K^+
- **Inward rectifier**
  - P domain: "Selectivity filter"

Diagrams	○ 2 Flanking transmembrane region ○ Homo- or heterooligomers in membrane ○ Ion selectivity: $K^{\pm}$ • **Gap junction channels** ○ 6 polypeptide subunits ○ Each subunit has 4 membrane spanning regions • **ATP gated channels**: 3 Homologous polypeptide subunits

CHLORIDE CHANNELS

Principles
Disorders

Chloride channels: Principles[14]

- Anion channels: General
  - Classification schemes
    - Localization: Plasma membrane vs. vesicular
    - Single-**channel** conductance
    - Mechanism of regulation
    - Molecular structure
  - Function
    - Allow the passive diffusion of negatively charged ions along electrochemical gradient
    - May conduct other anions (e.g., I^- or NO_3^-) better than Cl^-
    - Often called Cl^- channels because Cl^- is the most abundant anion in organisms
    - May perform functions in plasma membrane or in membranes of intracellular organelles
    - Functions often related to transport of charge
    - Cl^- does not seem to play a role as intracellular messenger
  - Cl^- **channel** gating may depend on
    - Transmembrane voltage: Voltage-gated channels
    - Cell swelling
    - Binding of signaling molecules: Ligand-gated anion channels of postsynaptic membranes
    - Ions [e.g., Anions, H^+ (pH), or Ca^{++}]: Intracellular Cl^- concentration may regulate **channel** activity
    - Phosphorylation of intracellular residues by various protein kinases
    - Binding or hydrolysis of ATP
- General function of Cl^- channels in tissues
  - Muscle: Contributes to resting conductance; Stabilizes resting potential; Loss produces myotonia
  - Smooth muscle: Opening of Cl^- channels leads to depolarization
- Structural classes of Cl^- channels
  - Extracellular ligand-gated Cl^- channels (ELG)
    - 4 transmembrane domains in each subunit
    - Receptors function as pentamers
    - Types
      - Post synaptic
      - GABA & Glycine receptors
  - Cystic fibrosis transmembrane conductance regulator (CFTR)
    - Family: ATP-binding cassette (ABC) transporters
    - Transmembrane domains: 2 Sets of 6

- Sets separated by a cytoplasmic region with nucleotide binding fold (NBF1) & regulatory R domain
- **Channel** opening is controlled by
  - Intracellular ATP
  - Phosphorylation by cAMP- or cGMP-dependent kinases

- Voltage-gated chloride channels (CLC)
  - Membrane-associated part of CLC channels is composed of 17 α-helices
    - Helix A is not inserted into the membrane
    - Most of the helices are not perpendicular to the membrane, but severely tilted
    - Helices may not span the width of the bilayer
  - Carboxy terminus of eukaryotic CLC proteins has two CBS domains
    - Unspecified role in protein-protein interaction
  - CLC channels are dimers: Each monomer has one pore (double-barreled channels)
  - CLC-K proteins
    - Associate with the β-subunit barttin which spans the membrane twice
  - CLC **channel** types
    - CLC-1
      - Skeletal muscle, Placenta
      - Voltage stabilization
      - Mutation disorders: Myotonia; Paramyotonia
    - CLC-2
      - Ubiquitous
      - Cell volume regulation
      - Activated by hyperpolarization, cell swelling & acidic pH
      - Mutation disorders: Idiopathic generalized epilepsies
    - CLC-3
      - Brain, Kidney (Type B intercalated cells), Skeletal muscle, Lung, Retina
      - Intracellular
      - Endosomes & Synaptic vesicles
      - Knockout: Degeneration of hippocampus & retina
    - CLC-4
      - Muscle, Brain, Heart, Kidney, Retina
      - Vesicular **channel**
    - CLC-5
      - Kidney (Type A intercalated cells)
      - Endosomal **channel**
      - Renal endocytosis
      - ? Cl^- reabsorption
    - CLC-6
      - Ubiquitous
      - Intracellular
    - CLC-7
      - Brain; Testes; Skeletal muscle; Kidney
      - Lysosomal
      - Mutations: Osteopetrosis
    - ClC-0: *Torpedo* electric organ Cl^- **channel**
    - ClC-K/barttin channels: Transepithelial transport in kidney & inner ear
      - CLC-K1 (CLCN-KA): Kidney
        - Transepithelial Cl^- transport
        - Location: Thin ascending limb of Henle loop in renal inner medulla
        - Plays role in urine concentration
      - CLC-K2 (CLCN-KB)
        - Kidney
        - ? Cl^- reabsorption

        - Bartter syndrome types 3 & 4
    - Nucleotide sensitive chloride **channel** (CLNS1A): Volume sensitive
    - Chloride intracellular channels
        - General
            - Location: Nuclear or Plasma membrane
            - No membrane spanning domains
            - Found vacuolar organelles
            - Function: Electrolyte composition & Acidification of intravesicular spaces
        - CLIC1: Nuclear
        - CLIC2: Skeletal muscle; Fetal liver
        - CLIC3: Plasma membrane; Interacts with Erk7
        - CLIC4: Brain, Heart, Placenta, Skeletal muscle
        - CLIC5: Heart; Skeletal muscle
    - **Calcium** activated: Mediate a **calcium**-activated chloride conductance
        - CLCA1: Intestinal basal crypt epithelium & goblet cells
        - Lung-endothelial cell adhesion molecule-1 (Lu-ECAM-1)
        - CLCA2: Lung & trachea
            - Inhibitors: DIDS, Dithiothreitol, Niflumic acid, Tamoxifen
        - CLCA3: ? Does not function as a **channel** protein
    - Also see
        - Anion transporters
        - Na^+, K^+, Cl^- Co-transporters

Chloride channels: Disorders

- Myotonia congenita (CLC-1)
    - Dominant (Thompsen)
    - Recessive (Becker)
- Myotonic Dystrophy (DM1; DM2): Expanded CUG or CCUG repeats
    - Retained in nucleus
    - Disrupt splicing of chloride **channel** (ClC-1) pre-mRNA
- Epilepsy
    - CLC-2
        - Absence epilepsy: Childhood & Juvenile
        - Myoclonic epilepsy, Juvenile
        - Epilepsy with grand mal seizures on awakening
    - Gamma-aminobutyric acid (GABA) receptors
        - GABA receptor, γ-2 subunit(GABRG2); Chromosome 5q31.1-q33.1; Dominant
            - Generalized epilepsy with febrile seizures plus, type 3
            - Childhood absence epilepsy
            - Febrile seizures
- Renal tubular disorders (CLC-5)
    - Hypercalciuric nephrolithiasis
    - X-linked recessive Nephrolithiasis
    - Dent disease
- Nephrogenic diabetes insipidus (Mouse): (CLC-KA)
- Bartter's syndrome (CLC-KB)
- Cystic fibrosis (Epithelial chloride **channel**)
- Osteopetrosis, infantile, malignant: CLC-7
- Angleman or Prader-Willi: $GABA_AB_3$ receptor subunit
- SLC26A4: Transporter of chloride & iodide
    - Non-syndromic deafness, congenital
    - Pendred syndrome

- Alcohol non-tolerant rat: $GABA_{\alpha 6}$ receptor subunit
- Glioma
  - Cl^- channels upregulated in glioma cells
  - High grade (poorly differentiated) tumors also lose $Na^{\pm}$ channels
- Toxin: Chlorotoxin (Scorpion)

SODIUM CHANNELS

Sodium channels: Principles

- Types: Voltage-gated; Non-voltage-gated; Exchangers
  - Voltage-gated Na^+ channels
    - Function
      - Generate current to overcome membrane capacitance & resistance
      - Generate (Upstroke) & Propagate self-regenerating action potential
    - Associated proteins
      - $Ankyrin_G$
      - Neurofascin
    - Localization
      - Clustered at axon initial segments, nodes of Ranvier & Post-synaptic folds of NMJ
      - $Ankyrin_G$ necessary for clustering
    - Structure: Often $\alpha\beta1\beta2$ heterotrimer
    - α subunits
      - Structure: 4 repeated domains; Each with 6 membrane spanning subunits; Glycosylated
      - Function: Forms ion pore; May be sufficient for funtional Na^+ **channel**
      - Voltage sensor on 4th transmembrane domain
      - Different subtypes: Specific tissue localization
        - SCN1A ($\alpha1$; I): $Na_v1.1$
          - High levels in brain
          - Blockers: Tetrodotoxin; Saxitoxin
        - SCN2A1 ($\alpha2$; II): $Na_v1.2$
          - Most abundant form in brain
          - Peripheral nerve: Initial segment; Nodes of Ranvier
          - Blockers: Tetrodotoxin; Saxitoxin
          - Mutations: Seizure disorder
        - SCN2A2
          - High levels in brain
        - SCN3A ($\alpha3$; III): $Na_v1.3$
          - High levels in brain
          - Blockers: Tetrodotoxin; Saxitoxin
          - Downregulated by: NGF; GDNF
        - SCN4A ($\mu1$): $Na_v1.4$

- High levels in muscle
- Blockers: Tetrodotoxin; μ-conotoxins GIIIA, GIIIB, GIIIC
- Diseases: Hyperkalemic periodic paralysis, Paramyotonia, Myotonia, Myasthenia

- SCN5A: $Na_v1.5$
  - Heart; Initial phase of upstroke on EKG
  - Skeletal muscle: Denervated
  - Tetrodotoxin & Saxitoxin resistant
  - Diseases
    - Long QT syndrome 3
    - Progressive cardiac conduction defect (PCCD2; Lenegre-Lev disease)
    - Congenital non-progressive heart block
    - Sudden infant death: S1103Y mutation, especially homozygosity
    - Sudden unexplained nocturnal death
    - Idiopathic ventricular fibrillation
    - Congenital sick sinus syndrome
- SCN7A: Na_x
  - Heart; Uterus; Skeletal muscle (Fetal & Denervated)
- SCN8A (PN4): $Na_v1.6$
  - Brain & Spinal cord
  - Primary **channel** at
    - Nodes of Ranvier: Mature
    - Axon: Initial segments
  - Physiology
    - Currents: Fast transient; Smaller persistent (Contribute to intrinsic burst activity)
    - Upregulation: Might produce hyperexcitability
  - Diseases: motor endplate disease (med) mouse; dmu mouse
- SCN9A (PN1): $Na_v1.7$
  - Similar to rat PN1: Dorsal root ganglia; Neuroendocrine (Adrenal & Thyroid)
  - Tetrodotoxin (TTX) sensitive
  - Disease: Familial erythermalgia
- SCN10A (PN3; SNS): $Na_v1.8$
  - Depolarized activation potential
  - Kinetics: Slow inactivation; Rapid repriming
  - Tetrodotoxin resistant
  - Location: Small sensory neurons in PNS
  - Upregulated by: NGF; GDNF
  - Clinical association: Pain sensitization
- SCN11A (NaN): $Na_v1.9$
  - Spinal sensory neurons: Dorsal root & Trigeminal ganglia
  - Tetrodotoxin resistant
  - Upregulated by: NGF; GDNF
  - **Channel** openining (rapid) stimulated by BDNF via BDNF binding to TrkB receptor
  - Clinical association: Pain sensitization
- Other: Na-G (Glia); hNa_v (Heart)

- β subunits
  - General function: Regulate ion-conducting α-subunits
  - SCN1B (β1)
    - Binding to α-subunit by non-covalent linkage
    - Associates with different forms of α-subunit in brain, heart & skeletal muscle
    - Provides inactivation kinetics to Na^+ **channel**

- Disease: Generalized epilepsy with febrile seizures +
- SCN2B (β2)
  - Binding to α-subunit by disulfide bond covalent linkage
  - 1 transmembrane domain
  - N-terminal similarity to contactin, a neural adhesion protein
  - CNS localization
- SCN3B
  - Location: Brain, especially hippocampus; Adrenal; Kidney
  - Function
    - Hyperpolarizing shift in voltage-dependence of inactivation
    - Modulates α subunit: Increases fraction of channels operating in fast-gating mode
    - SCN3B inactivates **channel** opening more slowly than SCN1B
- SCN4B
  - Alters **channel** properties of SCN2A
    - Shifts the voltage dependence of activation in toward hyperpolarization
    - No change in voltage dependence of inactivation

- Non-voltage-gated Na^+ channels: Amiloride sensitive
  - SCNN: Epithelial **sodium channel**
    - Functions
      - Control Na+ resorption
      - Role in taste perception
    - Heterotrimer: αβγ or δβγ
    - Structure: 2 transmembrane domains
    - Blockade: Amiloride
    - Subunits
      - SCNN1A (α): Pseudohypoaldosteronism I
      - SCNN1B (β): Pseudohypoaldosteronism (Liddle syndrome)
      - SCNN1D (δ)
      - SCNN1G (γ): Pseudohypoaldosteronism (Liddle syndrome)
  - Degenerins: Epithelial Na^+ **channel** family
    - Characteristics
      - Amiloride sensitive
      - Neuronal: Brain; Spinal cord
      - Function: Mechanosensory channels
      - Permeable to Na^+, K^+ & Li^+
      - Mutations: Activate channels & cause neurodegeneration in C. elegans
    - Types: Acid-sensing ion channels
      - BNAC1 (ACCN1): Cation **channel**; Abundant in brain neurons
      - BNAC2 (ACCN2): Brain neurons
      - BNAC4: Expressed in pituitary gland
    - See: Proton-gated ion channels
- **Sodium**/Hydrogen exchangers
  - Function: Eliminate acids from intracellular space
  - Activation: Low intracellular pH
  - Inhibition: Amiloride
  - Types
    - NAH1 (SLC9A1)
      - Ubiquitous expression
      - Functions: Regulation of intracellular pH & cell volume
      - Mouse mutant
        - Slow wave epilepsy (3 Hz); Ataxia
        - Pathology: Cerebellum (Deep nuclei) & brainstem
    - NAH2 (SLC9A2)

        - Location: Intestine; Kidney
        - Function: Na^+ ion absorption into mitochondria
    - NAH3 (SLC9A3) : Insensitive to amiloride
    - NAH4 (SLC9A4) : Stomach
    - NAH5 (SLC9A5) : Brain, Testis, Spleen, Skeletal muscle
    - SLC9A6 :
        - Location: Brain & Skeletal muscle > Other tissues
        - Function: ? Mitochondrial
    - SLC9A7 :
        - 12 N-terminal alpha-helical hydrophobic membrane-spanning segments
        - Location: Occipital lobe; Skeletal muscle; Secretory tissues
        - Functions
            - Amiloride-insensitive, benzamil-sensitive influx of Na^+ or K^+ for H^+
            - Cation homeostasis & function of the trans-Golgi network
- Other Na^+ exchangers
    - SLC5A
        - **Sodium**-glucose transporters
            - SLC5A1 : Glucose/Galactose malabsorption
            - SLC5A2 : Renal
        - **Sodium**/myoinositol cotransporter (SLC5A3)
        - Na^+/I^- symporter (SLC5A5) : Congenital hypothyroidism
        - **Sodium**-dependent multivitamin transporter (SLC5A6)
    - SLC24
        - **Sodium/Potassium/Calcium** exchanger (SLC24A1)

- External link: UCLA anesthesia

Sodium channels: Disorders

- Skeletal Muscle
    - SCN4A, α-subunit
        - Hyperkalemic periodic paralysis
        - Hypokalemic periodic paralysis
        - Paramyotonia congenita
        - Myotonia Fluctuans
        - Myotonia Permanens
        - Acetzolamide-responsive myotonia
        - Malignant hyperthermia
        - Myasthenic syndrome
    - Monensin overdose: Rhabdomyolysis
    - SCN8A (PN4)
        - Diseases: motor endplate disease (med) mouse; dmu mouse
- Peripheral nerve
    - Localization of voltage-gated Na^+ channels
        - RI: Soma
        - RII: Axonal initial segment & nodes of Ranvier
    - Hereditary
        - SCN9A : Familial erythermalgia
    - Immune
        - Anti-GM1 ganglioside antibodies
            - Multifocal Motor Neuropathy
            - Acute motor axonal neuropathy
        - ? Guillain-Barré & CIDP

- Nerve injury
  - Neuromas: Accumulation of Na^+ channels on axons in neuromas
  - Nerve transection
    - Down regulation:SCN10A; SCN11A
    - Up regulation: SCN3A
      - Contributes to hyperexcitability (Allodynia; Hyperesthesia)
- Na^+ **channel** toxins

- Brain & Spinal Cord
  - α subunit: SCN1A: Fever associated seizures
    - Generalized epilepsy with febrile seizures plus, Type 2 (GEFS+2)
      - Mutations
        - Missense
        - Location: S4 & S5 transmembrane segments
        - Mutation action: Disrupts **channel** inactivation
      - Inheritance: Dominant
      - Clinical: Mild seizure disorder
    - Myoclonic Epilepsy of Infancy: Severe
      - Most mutations
        - *De novo*
        - Truncating type
        - Disease mechanism: ? Haploinsufficiency
      - Clinical: Ataxia; Severe seizures (Onset 2 to 6 months); Mental retardation
    - Infantile spasms
  - α subunit: SCN2A1
    - Seizure disorders
      - Benign familial neonatal-infantile
      - Febrile & Afebrile
    - Seizure disorder in mice
      - Mutation action: Disrupts **channel** inactivation
  - α subunit: SCN8A
    - Motor endplate disease (med) in mice
  - β subunit: SCN1B
    - Generalized epilepsy with febrile seizures + (GEFS+1)
    - Mutation action: Disrupts **channel** inactivation
- Cardiac - α subunit: SCN5A
  - Long QT Syndrome (LQT3)
  - Idiopathic ventricular fibrillation (IVF)
  - Progressive cardiac conduction defect (PCCD2; Lenegre disease)
    - Clinical syndrome: Syncope; Right bundle branch block
    - Genetics
      - DelG5280
      - Other locus: Chromosome 19q13.3
  - Non-progressive congenital heart block
- Epithelial, Nonvoltage-gated, α & β subunits
  - SCNN1A & SCNN1B
  - Pseudohypoaldosteronism (Liddle's syndrome; Hereditary hypertension)
- Thyroid
  - Na^+/I^- symporter (SLC5A5): Congenital hypothyroidism
- Endocrine
  - **Sodium**-glucose transporter 1 (SLC5A1): Glucose/galactose malabsorption
- Neoplasms: Voltage gated Na^+ channels
  - Present in small cell lung cancer cell lines
  - Associated with invasion by prostate cancer cells *in vitro*.

- Na^+ **channel** Toxins[1]
  - Guanidinium: Saxitoxin; Tetrodotoxin
  - Polypeptide
    - Scorpion toxins (α & β)
    - Sea anemone toxins
    - Conotoxins (δ & μ)
  - Lipophilic:
    - Brevetoxins (Red tide), Veratridine & Aconitine: Open Na^+ channels
    - Batrachotoxin; Ciguatoxin; Grayanotoxin
  - Drugs: Lidocaine; Phenytoin

CALCIUM CHANNELS

Voltage-gated Ca^{++} entry channels: Principles

- Ca^{++} channels contain 4 or 5 distinct subunits
- α-1 subunits
  - Subtypes: Numerous; Different tissue & peptide specificity
    - α_{1A} (CACNA1A; P/Q type; $Ca_v2.1$): Brain, Motor neurons, Kidney
    - α_{1B} (CACNA1B; N-type; $Ca_v2.2$): CNS, PNS
    - α_{1C} (CACNA1C; L-type; $Ca_v1.2$): Heart, Fibroblasts, Lung, Smooth muscle
    - α_{1D} (CACNA1D; L-type; $Ca_v1.3$): Brain, Pancreas, Neuroendocrine
    - α_{1E} (CACNA1E; R-type; $Ca_v2.3$): Brain, Muscle (NMJ)
    - α_{1F} (CACNA1F; $Ca_v1.4$): Retina
    - α_{1G} (CACNA1G; T-type; $Ca_v3.1$)): Brain
    - α_{1H} (CACNA1H; T-type; $Ca_v3.2$): Kidney; Liver; D hair mechanoceptors
    - α_{1I} (CACNA1I; T-type; $Ca_v3.3$): Brain
    - α_{1S} (CACNA1S; L-type; $Ca_v1.1$): Skeletal muscle; L-type DHP receptor
  - Location: Transmembrane
  - Functions
    - Voltage sensor
    - Ca^{++} selective pore: Conductance
  - Structure: Consists of 4 internal repeated domains (I-IV)
    - Domain I: responsible for **channel** activation kinetics
    - Each domain contains 6 α-helical transmembrane regions (S1-S6)
    - S4: Positively charged; Forms part of the voltage sensor

- 2 additional domains between S5 & S6: Form pore region of **channel**
- Verapamil & nifedipine bind
  - Helix 5 & 6 regions of domain III
  - Sequence after helix 6 of domain 4
- Non N-glycosylated
- Size: 160-273kD
- Lambert-Eaton myasthenic syndrome: IgG binds to domains II & IV of α_{1A} subunit

- Binding drugs: Dihydropyridines; Verapamil; Diltiazem

- Other subunits: Modulate **channel** functions
  - $\alpha_2\delta$ (CACNA2D1)
    - Cell location: Membrane spanning
    - Structure
      - α_2 & δ: Derived from same gene & Linked by disulfide bridges
      - Glycosylated extensively on extracellular domains
    - Size: 140-170kD
    - Function: Regulatory
      - Increases amplitude of Ca^{++} currents
    - Binding drug: Gabapentin
    - Skeletal muscle, Heart, Brain, Ileum
    - Related subunit types
      - CACNA2D2: Lung & Testis > Brain, Heart, Pancreas
      - CACNA2D3
      - CACNA2D4
        - Associated with coexpressed CACNA1C & CACNB3
        - Expressed at high levels in heart & skeletal muscle
  - β (CACNB)
    - Location: Intracellular; Cytoplasmic
    - Size: 52-78kD
    - Subtypes
      - β_1 (CACNB1): Skeletal muscle, Brain, Heart, Spleen
      - β_2 (CACNB2): Brain, Heart, Lung, aorta
      - β_3 (CACNB3): Many tissues
      - β_4 (CACNB4): Brain, Kidney
    - Subtypes associate with different α_1 subunits in membrane
      - β_1 associates with α_{1S}
      - β_{1B} associates with α_{1B} & α_{1E}
      - β_4 associates with α_{1A}
    - Functions: Regulatory
      - Has cAMP-dependent protein kinase phosphorylation sites
      - Modifies current, voltage dependence & activation & inactivation
  - γ (CACNG)
    - Cell location: Membrane spanning; No cytoplasmic domain
    - Size: 32kD
    - Subtypes
      - CACNG1 (γ): Skeletal muscle, Neuronal, Lung
      - CACNG2 (γ2): Neuronal
      - CACNG3
      - CACNG4
      - CACNG5
      - CACNG6

        - CACNG7
        - CACNG8
    - Functions: Regulatory
        - Produce small increase in peak Ca^{++} current & activation rate
        - Shift activation to more hyperpolarized membrane potentials
        - Auxiliary subunits AMPA-type glutamate receptor
            - CACNG types: 2,3,4,8
            - Regulate
                - Early intracellular transport
                - Synaptic targeting & anchoring
                - Ion **channel** functions
        - Mouse disorders
- Ca^{++} **channel** classes (Voltage-gated): Related to α-1 subunit
    - L-type (Long lasting) Ca^{++} **channel**
        - Subunits: α_{1C}, α_{1D}, α_{1F}, or α_{1S}, $\alpha_2\delta$, β_{3a}
        - Blockade
            - Sensitive to dihydropyridine (DHP) agonists and antagonists
            - Also blocked by phenylalkylamines (verapamil), benzothiazepines (diltiazem) & calciseptine
        - Activation: Strong depolarization
        - Inactivation by depolarization: Little
        - Localization
            - Skeletal muscle: α_{1S}
            - Brain (Neuronal soma & proximal dendrites): α_{1D}
            - Cardiac muscle: α_{1C}
            - Neuroendocrine: α_{1D}
            - Retina: α_{1F}
        - General function in muscle: Excitation-contraction coupling
            - Cav 1.1 (A1S): Skeletal muscle; Also acts as voltage sensor
            - Cav 1.2 (A1C): Heart & Smooth muscle
        - Diseases
    - N-type Ca^{++} **channel**
        - Subunits: α_{1B}, $\alpha_2\delta$, β_{1b}
        - Activation: Strong depolarization
        - Inactivation: Slow
        - Blockade: ω-conotoxins GVIA (Strong; Irreversible) & MVIIA
        - DHP insensitive
        - Neuronal localization: Presynaptic
        - Constituents: No γ subunit; Novel 100 kd subunit
        - Modulation[12]
            - Enigma homolog (PKC binding protein) interacts with PKCε & N-type Ca^{++} channels
            - Allows modulation of Ca^{++} **channel** activity by PKCε
        - Function: Transmitter release from presynaptic nerve terminals
        - Diseases
    - P-type Ca^{++} **channel**
        - Subunits: α_{1A}, $\alpha_2\delta$, β_{4a}
        - Activation: Strong depolarization
        - Inactivation: Slow
        - Blockade: Funnel web spider venom; ω-agatoxin IVA; ω-conotoxin MVIIC
        - Insensitive to DHP & ω-conotoxin GVIA
        - Localization

- Neuronal presynaptic
- High concentration of α_{1A} subunit in cerebellum: Purkinje cells
- Neuromuscular junctions

- Function: Transmitter release
- Diseases

- Q-type Ca^{++} **channel**
  - Subunits: α_{1A}, $\alpha_2\delta$, β_{4a}
  - α_{1A} subunit is splice variant of α_{1A} in P-type **channel**
  - Activation: Strong depolarization
  - Inactivation: Slow
  - Blockade: ? more sensitive to ω-conotoxin MVIIC than P-type
  - Location: Cerebellar granule cells; Hippocampal pyramidal neurons
  - Function: Transmitter release
- R-type Ca^{++} **channel**
  - Subunits: α_{1E} ($Ca_v2.3$), $\alpha_2\delta$, β_{1b}
  - Activation: High threshold, strong depolarization
  - Inactivation: Voltage dependent; Rapid kinetics
  - Blockade: SNX-482 peptide from African tarantula, *Hysterocrates gigas*
  - Functions
    - Transmitter release
    - Insulin release: 2nd phase
  - Associated protein: EFHC1
    - Increases R-type Ca^{++} **channel** currents
    - Mutations: Cause Juvenile myoclonic epilepsy
  - Location: Cerebellar granule neurons; Dendrites of hippocampal pyrimidal neurons
  - Action: Provide transient surge of Ca^{++} influx
- T-type (Transient) Ca^{++} **channel**[18]
  - Subunits
    - May be formed by single α_1 subunit
    - α_{1G} (Ca_v 3.1)
      - Localization: Brain
      - Currents generate burst mode firing of action potentials in thalamocortical relay neurons
      - Generation of GABA-B receptor-mediated spike-and-wave discharges
      - Fastest recovery from inactivation
    - α_{1H} (Ca_v 3.2)
      - Highest expression in kidney and liver; Also cardiac, neural, endocrine
      - Inhibition mediated by G protein β-2, γ-2 subunits
      - Neural: D hair mechanoceptors; Sympathetic ganglion neurons
      - Skeletal muscle: Embryonic; Associated with myoblast fusion
      - Slowest recovery from inactivation
      - Currents generate short burst firing
      - Missense mutations associated with: Childhood Absence Epilepsy in Northern China
    - α_{1I} (Ca_v 3.3)
      - Brain specific
      - LVA currents: Activate and inactivate much more slowly than typical T-type channels
      - Currents contribute to sustained electrical activities in neurons
  - Activation
    - By depolarization near resting potential
    - Low voltage activation (LVA) threshhold
    - Facilitated by strong depolarizing pulses

- Ca^{++} competes with protons for binding to **channel** selectivity filter
- Channels close slowly on repolarization of the membrane: Generates SD tail current
- Tiny & equivalent single-**channel** conductance of Ba^{++} & Ca^{++}
- Generates Low threshold **calcium** spikes (LTS) in brain

- Inactivation
  - Rapid
  - Steady-state inactivation occurs over a similar voltage range as activation
  - Window current: Small range of voltages where T-type channels can open, but do not inactivate completely
  - Rapid deinactivation
- Reactivation: Requires strong hyperpolarization
- T-type current regulation by G-protein coupled receptors
- Conductance: Low (~8pS)
- Blockade
  - Nickel ions: Especially Ca_V 3.2
  - Mibefradil
  - Kurtoxin: Peptide from South African scorpion, *Parabuthus transvaalicus*
  - Ethosuximide: Not at therapeutically relevant concentrations
  - Do not bind dihydropyridines
- Tissue localization: Cardiac & vascular smooth muscle; Nervous system
- Function
  - Rhythmic action (pacemaker) potentials in cardiac muscle & neurons
  - Burst firing mode of action potentials
  - Regulate intracellular Ca^{++} concentrations

- Physiology of Ca^{++} channels
  - Low threshhold: T-type
  - High threshhold (Activated at membrane potentials nearer 0 than resting): L, N, P-type

- **Other Ca^{++} channels**

- Ligand gated Ca^{++} entry channels
  - Ca^{++} transporting ATPase
    - ATP2A1 : Fast twitch skeletal muscle; Sarcoplasmic or endoplasmic reticulum
    - ATP2A2 : Slow twitch; 2 isoforms
      - SERCA2a: Heart & Slow-twitch skeletal muscle
      - SERCA2b: Smooth muscle & Nonmuscle tissues
    - ATP2B1 : Plasma membrane
    - ATP2B2 : Plasma membrane
    - ATP2B4
  - Disorders
- Capacitive Ca^{++} entry channels
- Intracellular activation channels
  - General features
    - Homotetrameric complexes
    - Structure: 6 putative transmembrane sequences (TMSs)
    - Putative **channel** lining region between TMSs 5 and 6
    - Covalently linked carbohydrate on extracytoplasmic loops of **channel** domains
  - Ca^{++} release channels: Ryanodine receptors (RYR)
    - Signalling system: Cyclic ADP-ribose (cADPR)
    - Second messangers: cADPR-Ca^{++}-Calmodulin
    - Stimuli: Ca^{++}; Caffeine; Ryanodine

- Inhibitors: Ryanodine
- Activated by activity of dihydropyridine-sensitive Ca^{++} channels
- Function: Signal amplifier
- Types
  - RYR1
    - Location: Skeletal muscle
    - Function: Involved in excitation-contraction coupling
    - Disorders
      - Malignant hyperthermia
      - Central core disease
      - Granulomatous myopathy: Antibodies vs RYR
  - RYR2: Cardiac
    - **Channel**
      - Structure: Tetramer comprised of
        - 4 RYR2 polypeptides
        - 4 FK506-binding proteins (FKBP1A)
      - Location: Sarcoplasmic reticulum
      - Function
        - Major source of Ca^{++} needed for cardiac muscle excitation-contraction coupling
        - **Channel** regulation by Protein kinase A (PKA)
        - Phosphorylation of RYR2
          - Dissociates FKBP1A from RYR2
          - Regulates **channel** open probability
      - RYR2 Macromolecular complex includes
        - FKBP1A
        - PKA
        - Protein phosphatases PP1 & PP2A
        - Anchoring protein, AKAP6
    - Disorders
      - ARVD2
      - Ventricular tachycardia, stress-induced polymorphic
  - RYR3: Brain
- Inositol-1,4,5-triphosphate (IP3) receptors
  - Location: Brain cell endoplasmic reticular (ER) membranes
  - Activated by increase intracellular levels of IP3
  - Structurally similar to ryanodine receptors
  - Cause release of intracellular Ca^{++} stores after stimulation of cell surface receptors
  - Function: Signal oscillation

- Other intracellular Ca^{++} channels[5]
  - Nicotinic acid adenine dinucleotide phosphate (NAADP) receptor
    - Signalling system: Cyclic ADP-ribose (cADPR)
    - Releases Ca^{++} from a thapsigargin-insensitive store
    - Second messenger & Stimulus: Nanomolar NAADP
    - Inhibition: High NAADP
    - Function: Signal trigger
  - Sphingolipid receptor (EDG1)
    - Signalling system: Sphingolipid pathways
    - Second messenger: ? Sphingosine-1-phosphate (S1P) or Sphingosyl-phosphorylcholine (SPC)

- **Ca^{++} sensors**

- Type A: Expressed in photoreceptor cells; function
  - Recoverin
  - Visinin
  - S-modulin
- Type B: Expressed in neurons
  - VILIP
  - Neuronal **calcium** sensor-1 (NCS1): Associated with secretory granules

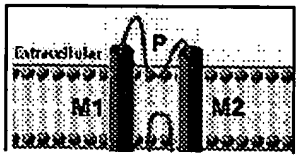
- **Ca^{++} channel disorders**

- L-type Ca^{++} **channel**, voltage-gated; Skeletal muscle (CACNL1A3 α_{1S}) & other subunits
  - Hypokalemic periodic paralysis (CACNL1A3 α_{1S} subunit)
  - Malignant Hyperthermia
    - CACNL1A3 α_{1S} subunit
    - ? $\alpha 2/\delta$ subunit
  - Long QT syndrome with syndactyly (Timothy syndrome): CACNA1C
  - X-linked congenital stationary night blindness: Incomplete form (CSNB2)
    - Ca^{++} **channel**, voltage-gated; α_{1F} subunit (CACNA1F): Retina specific subunit
  - Mouse models
    - Muscular dysgenesis mouse: Absent α_{1S} (CACNA1S) subunit
    - Deafness: CACNA1D deficiency
  - Toxins: Skeletal & smooth muscle
    - Polypeptides: Mamba snake (Calciseptine)
    - Dihydropyridines: Nifedipine...; Diltiazem; Verapamil
  - Self-biting & self-injurious behavior: Activation of CACNA1D containing L-type channels ((+/-)Bay K 8644)
- N-type Ca^{++} **channel**
  - Toxins: Polypeptide
    - ω-conotoxin SVIA
    - SNX-325 (Segestria spider toxin)
- P-type Ca^{++} **channel**, voltage-gated; Presynaptic terminal of motor axon
  - Lambert-Eaton Myasthenic Syndrome
  - ω-agatoxins: Especially IVA & IVB
  - CACNA1A (CACNL1A4) α_{1A} subunit [1]
    - Episodic ataxia type-2
      - Truncating mutations in repeat domain III
      - Probably produce non-functioning **channel**
      - Haploinsufficiency & mild cerebellar pathology
    - Familial hemiplegic migraine
      - Missense mutations in transmembrane segments
    - Progressive ataxia: SCA 6
      - Trinucleotide repeat expansion in intracellular region near carboxy terminus
      - Missense mutation: G293R
    - Mouse mutations: Loss of both alleles → prominent cerebellar degeneration
      - Tottering leaner
        - Recessive
        - Ataxia
        - Splicing mutation
        - Produces truncated protein
        - Physiology: Alteration in the whole-cell **calcium** current in Purkinje cells

    - Tottering
        - Recessive
        - Ataxia; Absence seizures (spike-wave)
        - Missense mutation in extracellular pore region of repeat domain II
        - Physiology at neuromuscular junctions
            - Greater Run-down of evoked acetylcholine release at high-rate stimulation
            - Greater Spontaneous acetylcholine release from presynaptic terminals
    - Rolling Nagoya
  - CACNB4 β4 subunit
    - R482X: Juvenile myoclonic epilepsy[6]
    - C104F: Generalized epilepsy & praxis-induced seizures; Episodic ataxia
- R-type Ca^{++} **channel**, voltage-gated; α_{1E} subunit
  - ? Hemiplegic migraine
- T-type Ca^{++} **channel**, voltage-gated
  - Greater current in reticular thalamic neurons in rat model of absence epilepsy
  - Missense mutations of CACNA1H associated with: Childhood Absence Epilepsy in Northern China[19]
- Ca^{++} release channels (Ryanodine receptors)
  - Ryanodine receptor 1
    - Malignant hyperthermia
    - Central core disease
    - Granulomatous myopathy: Antibodies vs RYR
  - Ryanodine receptor 2
    - Ventricular tachycardia, stress-induced polymorphic
    - Right ventricular dilated (ARVD) cardiomyopathy 2
- Ca^{++} transporting ATPase
  - ATP2A1
    - Brody myopathy
  - ATP2A2
    - Darier-White disease: Keratosis follicularis
  - ATP2B2
    - Deafwaddler (dfw) mouse: Deafness; Vestibular imbalance
- Mouse mutants: Other
  - β_1 null mutant mouse
    - Lacks excitation-contraction coupling: Dies at birth
  - Ca^{++} **channel**, voltage dependent, β4 subunit (CACNB4)
    - Lethargic (lh) mouse: Seizures; Ataxia
  - Ca^{++} **channel**, voltage dependent, γ2 subunit (CACNG2)
    - Stargazer: Absence epilepsy; Head tossing; Ataxia
    - Waggler: Absence epilepsy; Head tossing; Ataxia
  - CACNA2D2: Ducky mouse; Ataxia & Slow wave seizures

POTASSIUM CHANNELS

- **Principles & Types of K^+ Channels**
  - Structure[4]
    - **K^+ channel**
      - Inner & Outer membrane face
        - Layers of aromatic amino acids: Tryptophan; Tyrosine
        - Form cuff around pore
        - Pull pore opening like springs
      - Selectivity filter
        - Narrow region near outer face of membrane
        - Contains glycine-tyrosine-glycine residues
        - Lined by carbonyl backbone of conserved amino acids
        - ? Carbonyl oxygens act as surrogate H_2O: Coordinate 2 dehydrated K^+ ions sitting in line in **channel**
      - Ions travel through **channel** in single file
    - Voltage gated K^+ channels (Kv)
      - 6 Transmembrane (TM) regions (S1-S6)
      - 4 Subunits surround central pore (TM **channel**): S5 & S6 regions of each subunit
      - Selectivity filter (P region): Hydrophobic sequence between last 2 TM regions; Contains Gly-Tyr-Gly
      - Voltage sensing: Multiple positively charged amino acids in 4th TM region (S4)
    - Inwardly rectifying K^+ channels (Kir)
      - 2 Transmembrane regions (M1 & M2): Correspond to last 2 TM regions (S5 & S6) in Kv channels
      - 4 Subunits surround central pore (TM **channel**)
      - P region: Separates M1 & M2
      - Non-conducting at positive membrane potentials
  - K^+ **channel** functions: Often voltage-sensitive
    - Delayed rectifier K^+ channels
      - Delayed activation; Slow inactivation
      - Allows efficient repolarization after action potential
      - Blockers: 4-aminopyridine; Dendrotoxins; Phencyclidine; Phalloidin; 9-aminoacridine; Margatoxin; Imperator toxin; Charybdotoxin
      - Structure: Tetramer of α-subunits ± β-subunit
    - Inward rectifier K^+ channels (Kir)
      - General properties
        - K^+ **channel**: Greater tendancy to allow **potassium** to flow into cell rather than out
        - Voltage dependance: Regulated by concentration of extracellular **potassium**
        - Inward rectification mainly due to the blockage of outward current by internal magnesium
        - Can be blocked by external Ba^{++}
        - Subcellular location: Integral membrane protein
        - Activity of Kir channels is dependent on interactions with phosphatidylinositol 4,5-bisphosphate (PIP2)
      - Functions
        - Maintain resting membrane potential near equilibrium potential for K^+ ions
        - Contribute to cell excitability
        - Tissues: Excitable; Heart, Brain, Skeletal muscle
        - Non-conducting at positive membrane potentials
      - Typical Kir: Large family
        - Roles in excitability & resting conductance of muscle cells and neurons



- Some ATP-sensitive or GTP-activated
- Structure
  - 2 membrane-spanning domains in each subunit (M1 & M2)
    - Correspond to last 2 TM regions (S5 & S6) in Kv channels
  - N-terminal domain: Intracellular
  - C-terminal domain: Intracellular
  - No voltage sensor in voltage-gated channels
  - Homologous to regions in voltage-gated K^+ **channel**
    - Transmembrane regions 5 (M1) & 6 (M2)
    - P region
      - Separates M1 & M2
      - Pore helix
      - Loop region: Major ion selectivity filter; Amino acid TVGYG core
  - Subunit clustering
    - Homotetramers or Heterotetramers
    - 4 Subunits surround central pore (TM **channel**)
- Currents
  - Large inward at potentials negative to K^+ equilibrium potential
  - Small outward currents at more positive potentials
- Blockers: LY97241; Gaboon viper venom; Sr^{++}; Ba^{++}; Cs^+
- Regulation: External K^+; Internal Mg^{++}; Intracellular polyamines, ATP or G-proteins

- Human ether-a-go-go (HERG; KCNH) : Atypical with 6 transmembrane domains
- See: Specific **channel** types; Disorders

- Ca^{++} sensitive K^+ channels: Generate membrane potential oscillations; Afterhyperpolarization
  - General structure & function[15]
    - 4 protein subunits
    - Each subunit contributes one membrane-spanning segment (Helical structure) to the pore lining
    - External surface: Contains selective K^+ filter; Formed by backbone carbonyls
    - Inner cavity: Accommodates a hydrated K^+ ion
    - Cytoplasmic side of **channel**
      - Subunit helices form a bundle of RCK domains which act as gate
      - RCK domains have fixed & flexible interaction domains
      - 2 Ca^{++} ions bind to flexible RCK interaction domains & regulate gate
  - High conductance (BK)
    - Gated by internal Ca^{++} and membrane potential
    - Unit conductance: 100 to 220 picoSiemens (pS)
    - Openers: NS004; NS1619; DHS-1
    - Blockers: Iberiotoxin; (+)-tubocurarine; Charybdotoxin; Noxiustoxin; Penitrem-A; TEA
  - Intermediate conductance (IK)
    - More sensitive to Ca^{++} than BK channels
    - Gated only by internal Ca^{++} ions
    - Unit conductance: 20 to 85 pS
    - Blockers: Cetiedil; Trifluoroperazine; Haloperidol
  - Small conductance (SK): Minimal voltage-gating (KCNN; ISK-family)
    - More sensitive to Ca^{++} than BK channels
    - Gated only by internal Ca^{++} ions
    - Voltage independent
    - Unit conductance: 2 to 20 pS
    - Blockers: Apamin ; Leiurotoxin 1 ; (+)-tubocurarine
- ATP-sensitive K^+ channels[25]

- General
  - Inhibitory effect: ATP
    - ATP acts from the cytoplasmic face of membrane
    - ATP reduces K^+ **channel** open probability
  - Facilitation: Nucleoside diphosphate
- Components
  - K+ pore: Kir6 subunits
    - KCNJ8
    - KCNJ11
  - Regulatory subunits: Sulphonylurea receptors (SURs)
    - Members of the ATP-binding cassette (ABC) family
    - SURs: SUR1 & SUR2
- Properties
  - Inwardly rectifying; pH sensitive
  - Not voltage-dependent
- Openers: Levcromakalim; Diazoxide; Aprikalim; Pinacilil
- Blockers: Glibenclamide; Tolbutamide; Phentolamine: Ciclazindol; Lidocaine
- Structure: Tetramer of 2-transmembrane subunits
- Functions
  - Couples membrane K^+ conductance (membrane potential) of cell to metabolic state
  - Senses intracellular nucleotide concentrations
  - Role in many tissues: Response to metabolic changes such ashypoxia, ischaemia
  - Glucose concentration sensor in β-cells
    - Underly insulin secretion due to increase in blood glucose concentration
  - Heart
    - Protective function: Response to hypoxia or ischaemia
    - Underlie responses to metabolic or catecholamine stress
  - Skeletal muscle
    - Roles in fatigue & glucose uptake

- Na^+ activated K^+ channels
  - Voltage-insensitive
  - Blockers: Mg^{++}; Ba^{++}
- Cell volume sensitive K^+ channels
  - Activated by increased cell volume
  - Blockers: Quinidine; Lidocaine; Cetiedil
- Type A K^+ channels: Rapid activation & inactivation
  - Blockers: 4-aminopyridine; Quinidine; Mast cell degranulating peptide; Phencyclidine; Dendrotoxins
  - ? Regulation of fast repolarizing phase of action potentials: Delay spiking
  - Structure: Tetramer of α-subunits + intracellular β-subunits
  - β-subunits may confer rapid inactivation
- Receptor-coupled K^+ channels
  - Muscarinic-inactivated
    - Slow activation; Non-inactivating; Non-rectifying
    - Openers: Somatostatin; β-adrenoceptor agonists
    - Blockers: Ba^{++}; Bradykinin
  - Atrial muscarinic-activated
    - Inward rectifying
    - Blockers: Ba^{++}; Cs^+; 4-aminopyridine; TEA; Quinine
    - Structure: Tetramer of KCNJ3 & KCNJ5

- Subunits: Molecular families
  - Voltage-gated K^+ channels (Kv)

- 6 transmembrane domains
- Activated by depolarization
- Present in both excitable and nonexcitable cells
- Functions
  - Regulate resting membrane potential
  - Control of the shape and frequency of action potentials
- α subunits: 2 types
  - Functional by themselves
  - Electrically silent: Modulate activity of functional α subunits
- Types
  - KCNA (Shaker): KCNA 1, 5 & 6 genes located in cluster on Chromosome 12p13
    - KCNA1 (Kv1.1)
      - Location: Presynaptic & Juxtaparanodal membranes
      - Delayed rectifier
      - Disease: Episodic Ataxia/Myokymia Syndrome (EA1)
    - KCNA2 (Kv1.2):
      - Heterotetramer of **potassium channel** proteins
      - Location on axons: Presynaptic & juxtaparanodal
      - Molecular localizations
        - N-terminus: Role in determining rate of **channel** inactivation
        - Tail: Role in modulation of **channel** activity and/or targeting of the **channel** to specific subcellular compartments
        - Segment S4: Probably voltage-sensor
      - Delayed rectifier: Mediates voltage-dependent **potassium** ion permeability of excitable membranes
      - Binds PDZ domains of DLG1, DLG2 & DLG4
    - KCNA3 (Kv1.3): Skeletal muscle & Lymphocytes; Delayed rectifier
    - KCNA4 (Kv1.4): Presynaptic & Axonal & Fetal skeletal muscle; Type A rapidly inactivating
    - KCNA4L
    - KCNA5 (Kv1.5): Heart & Insulinoma; Delayed rectifier
    - KCNA6 (Kv1.6): Brain; Delayed rectifier
    - KCNA7
    - KCNA8 & KCNA9: see KCNQ1
    - KCNA10
    - KCNAB1: β1 subunit (Kv-β-1.1)
      - Modulates gating properties & amplitudes of Shaker channels
      - β3 subunit from alternate splicing of this gene
    - KCNAB2: β2 subunit (Kv-β-1.2)
    - KCNAB3

    - External link: UCLA anesthesia

  - KCNB (Shab)
    - KCNB1 (Kv2.1)
      - Locations: Soma; Proximal dendrite
      - Associates with: KCNG3, KCNG4, KCNV2
    - KCNB2 (Kv2.2)

  - KCNC (Shaw): Delayed rectifier
    - KCNC1 (Kv3.1): Brain, Skeletal muscle, Lymphocytes, Spleen
    - KCNC2 (Kv3.2): Brain
    - KCNC3 (Kv3.3):
      - Location: Brain, Liver

        - Disorder: SCA 13
    - KCNC4 (Kv3.4): Brain, Skeletal muscle
    - Function
        - Kv3 channels regulate synaptic transmission at parallel fiber-Purkinje cell synapse in cerebellum
        - Mice lacking Kv3.1 or Kv3.3 channels: Ataxic

- KCND (Shal): Molecular components of subthreshold-activating A-type K^+ currents
    - KCND1 (Kv4.1): Brain
    - KCND2 (Kv4.2)
        - Locations: Brain (Distal dendritic; Post-synaptic), Heart, Aorta
        - Modulated by Neuronal **calcium** sensor 1
        - Binds to Filamin C
    - KCND3 (Kv4.3): Cardiac ventricle transient outward **potassium** current I(to)

- KCNE
    - General
        - Components of slow voltage-gated channels
        - Structure: Small, single transmembrane domain-containing proteins
        - **Channel** function: Accessory subunits; Interact with & regulate activity of Kv channels
    - KCNE1 (minK protein)
        - Epithelial cell apical membrane
        - Codes for β subunit
        - Coassembles with KCNQ1 (KCNA8; KVLQT1) α subunit: Causes increased current amplitude
        - Forms slowly activating delayed rectifier K^+ (I_{Ks}) **channel**
        - Diseases: Jervell-Lange-Nielsen Syndrome; Long QT Syndrome 5
    - KCNE2 (minK related peptide 1)
        - Disease syndromes
            - Long QT syndrome 6
            - Atrial fibrillation
            - Ventricular fibrillation
            - Clarithromycin-induced arrhythmia
    - KCNE3
        - Interacts with α-subunit KCNQ1 in intestine crypt cells
        - KCNQ1/KCNE3 **channel**
            - Related to cyclic AMP-stimulated intestinal Cl^- secretion
            - ? Involved in secretory diarrhea and cystic fibrosis
        - Mutations may cause: Hypokalemic periodic paralysis
    - KCNE4
        - High tissue levels: Heart, skeletal muscle & kidney
    - KCNE1L
        - Expressed in heart, skeletal muscle, brain, spinal cord, and placenta
        - Deleted in AMME contiguous gene syndrome

- KCNF
    - KCNF 1: Large transcript abundant in heart; Smaller one brain specific

- KCNG
    - KCNG1: Large transcript abundant in placenta & brain; Smaller one in skeletal muscle
    - KCNG2

- Expressed in myocardium
- Subunits in delayed-rectifier type channels
- ? Contribute to cardiac action potential repolarization

- KCNG3 (Kv10.1)
  - Functions as γ subunit: Modifies Kv2.1 **channel** activity
  - Subcellular location: Plasma membrane
- KCNG4 (Kv6.3)
  - Coexpressed with Kv2.1
  - Physiology
    - Accelerates time course of activation
    - Hyperpolarizes threshold for activation
    - Hyperpolarizes voltage dependence of inactivation

- KCNQ family[10]
  - General
    - Express M-current properties
      - Low-threshold, noninactivating, voltage-dependent K^+ current
      - Slowly opening & closing: 100x slower than channels associated with action potentials
      - Limits repetitive firing due to persistent depolarizing stimulus
    - Interactions: Can couple to M_1 muscarinic acetylcholine receptors
    - M-**channel** activity
      - Partially active in range of neuronal resting membrane potential
      - Further activated by membrane depolarizations
    - Inhibited by membrane receptors
      - Muscarinic AChR activity; Dopamine; Serotonin; Glutamate; Peptides
      - Receptors acting on G-protein receptors
    - General actions
      - Oppose epileptic activity: Restrain repetitive neuronal discahrges
      - Mediate transient increases in activity after release of ACh and other transmitters
    - Drug interactions
      - Linopirdine: Blocker of M-channels; Promotes ACh release
      - Retigabine: Opens M-channels
      - BMS-204352: Activates KCNQ channels; May reduce infarct size
    - Disorders
  - KCNQ1 (KCNA8; KVLQT1)
    - K^+ current: Slow delayed rectifier
    - Auxiliary subunit: KCNE1
    - Tissues: Heart, Pancreas, Cochlea (stria vascularis)
    - Disorders
      - LQT1 syndrome
      - Jervell-Lange-Nielsen Syndrome
      - Atrial fibrillation, Dominant
      - Short QT syndrome 2
  - KCNQ2
    - Locations
      - Brain: Somatodendritic pyramidal & polymorphic neurons; Cortex & Hippocampus
      - Sympathetic ganglia
      - Testis
    - Form M-channels with KCNQ3 & Calmodulin
    - Diseases

        - Benign neonatal epilepsy (EBN1)
        - Myokymia & Benign neonatal epilepsy
    - KCNQ3
        - Locations
            - Brain: Somatodendritic pyramidal & polymorphic neurons; Cortex & Hippocampus
            - Sympathetic ganglia
            - Spleen
            - Cochlea
        - Form M-channels with KCNQ2 & Calmodulin
        - Disease: Benign neonatal epilepsy (EBN2)
    - KCNQ4
        - Locations
            - Cochlea: Sensory outer, but not inner hair cells
            - Vestibular organs
            - Brainstem: Auditory nuclei
        - Disorder: Nonsyndromic sensorineural hearing loss, Dominant (DFNA2)
    - KCNQ5
        - Locations
            - Brain
            - Sympathetic ganglia
            - Skeletal muscle
        - Auxiliary subunit: KCNQ3
        - M-current

- KCNS family
    - General
        - Voltage-gated, Delayed rectifier
        - Brain, Spinal cord, Retina
        - No K^+ **channel** activity
        - Modulate activities of Kv2.1 (KCNB) & Kv2.2 α subunits
    - KCNS1 (K_V9.1)
        - Expressed in brain
        - No **potassium channel** activity by itself
        - Modulates activities of K_V2.1 (KCNB1) & K_V2.2
    - KCNS2 (K_V9.2)
        - Expressed in brain
        - No **potassium channel** activity by itself
        - Modulates activities of K_V2.1 (KCNB1) & K_V2.2
    - KCNS3 (K_V9.3)
        - Polymorphisms associated with airway hyperresponsiveness

- KCNV family
    - KCNV1 (Kv8.1)
        - Modifies kinetics of KCNB channels
    - KCNV2 (Kv11.1)
        - Coexpressed with Kv2.1
        - Disease: Cone dystrophy with supernormal rod electroretinogram
- Brain cyclic nucleotide gated K^+ channels (BCNG)[22]
    - Types
        - HCN1: Expression in brain; Activate rapidly
        - HCN2: Expression in brain & heart

        - HCN3 : Expression in brain; None in heart or skeletal muscle
            - Conducts **potassium & sodium** ions: 3:1 preference for **potassium**
            - Activity not modulated by intracellular cAMP
        - HCN4 : Expression in heart, brain (thalamus) & testis; Activate slowly
    - Properties
        - Permeability
            - Cations
                - K^+ 4x > Na^+
                - Current carried by Na^+ ions at typical membrane voltages
            - None to anions
        - Activation
            - Hyperpolarized membrane potentials
            - Slow time course
            - Sensitive to intracellular cyclic nucleotides
        - Modulated by: Cyclic nucleotides
        - Blockade by
            - Extracellular: Cesium; Capsazepine (Blocker of vanilloid receptors)
            - Intracellular: QX-314 (Lidocaine derivative); ZD7288 Bradycardiac agent)
        - Pacemakers: Generate rhythmic cellular activity
            - h-currents (I_h)
            - Allow cells to be rhythmically active over precise intervals of time
            - Tissue location: Cardiac; Neuronal
        - Other functions
            - Dendritic integration
                - Temporal summation of distal synaptic inputs
                - Dampens cellular responses to inhibitory synaptic input
                - Allows rapid resumption of tonic firing
            - Synaptic release
                - Can facilitate neurotransmitter release
                - Response to repetitive action potentials
            - Primary sensory reception
                - Expressed in taste cells: Receptors for sour taste
                - Thermoreception
- External link: UCLA anesthesia

- **Potassium** channels: Inwardly rectifying (Kir)
    - General properties
    - General families
        - Kir2.0
            - Action: Strong rectification
            - Function: Maintenance & control of cell excitability
            - Interactions: Among all Kir2 channels; SAP97
        - Kir3.0 (GIRK)
            - KCNJ subtypes: 3, 5, 6, 9
            - G-protein gated
            - Tetramers form K_G channels
            - Expressed throughout CNS
            - Acetylcholine-responsive inward rectifier composed of Kir3.1 & Kir3.4
        - Kir1.0/4.0: K+ transporters
        - Kir5.1
            - Homomeric assembly with PSD-95
            - Related to PKA-mediated signalling
        - Kir6

        - ATP sensitive
        - Associates with sulfonylurea receptors
    - Kir7
        - Very low single **channel** conductance
        - Low sensitivity to block by external Ba^{++} and Cs^{+}
        - No dependence of inward rectification properties on internal blocking Mg^{++}
        - Helps to set membrane potential
- Kir Types: Large family
    - KCNJ1 (Kir1.1):
        - Highest tissue levels: Kidney & Pancreas islets
        - Activation: Internal ATP
        - Blockade: External Ba^{++}
        - Disease: Bartter syndrome (Antenatal)
    - KCNJ2 (Kir2.1)
        - Tissue localization: Brain, Heart, Skeletal muscle, Lung, Kidney, Placenta
        - Strong inward rectifier
        - **Channel** compositions
            - Channels are often homotetramers
            - Subunit associations: Other Kir2; SAP97
        - Polarized distribution: Enables channels to transport K^{+} ions to appropriate regions
        - Role
            - Generation of action potential waveform + Excitability in muscle & neural tissue
            - Prevents excessive loss of K^{+} during plateau phase of cardiac action potential
            - Allows outward K^{+} flux during terminal repolarization & diastole
            - Development: Myoblast fusion; Bone morphogenesis
        - G-protein enhanced current
        - Blocked by Ba^{++} or Cs^{+}
        - Diseases
            - Andersen syndrome
            - Short QT syndrome 3
    - KCNJ3 (Kir3.1)
        - Subunit associations
            - KCNJ5, KCNJ6 & KCNJ9
            - Homotetramers do not form functional channels
        - Muscarinic & G-protein linked
        - Role: Heartbeat regulation
    - KCNJ4 (Kir2.3)
        - Subunit associations: Other Kir2; SAP97
        - Polarized distribution: Enables channels to transport K^{+} ions to appropriate regions
        - Modulated by arachidonic acid
        - Tissue localization: Heart; Skeletal muscle; Brain (Hippocampus)
    - KCNJ5 (Kir3.4)
        - Subunit associations: KCNJ3, KCNJ6
        - Tissue localization: Pancreas; Heart
        - Knockouts: **Channel** role in vagal regulation of heart rate & Spatial memory
    - KCNJ6 & KCNJ7 (Kir3.2)
        - Localization: Cerebellum
        - Associates with KCNJ9
        - Mediate inhibitory effects (outward currents) of opioids
        - Disorders: Weaver mouse
        - Knockouts: Seizures & Ethanol-induced behaviors
    - KCNJ8 (Kir6.1)

- Function: Regulation of vascular tone
- Controlled by G-proteins & ATP
- Knockout: Sudden death; Spontaneous ST elevation; Atrioventricular block

- KCNJ9 (Kir3.3)
  - Associates with KCNJ6
  - Mediate inhibitory effects (outward currents) of opioids with Kir3.2
  - Knockouts: Neuron membrane depolarization
- KCNJ10 (Kir1.2; Kir4.1)
  - Forms heterodimer with KCNJ16
  - ATP-dependent
  - Location: Glial; Muller cells (Retina); Kidney; Gastric parietal cells
  - Subcellular
    - Polarized distribution: Enables channels to transport K^+ ions to appropriate regions
    - Subcellular clustering associated with Dystrophin isoform dp71
    - Predominantly expressed in membranes adjacent to basement membranes
    - Laminin is necessary for surface expression of Kir4.1
    - Co-localizes with aquaporin-4 water **channel** in retinal glial cells
  - Functions
    - CO_2 chemoreception
    - ? Related to glial K^+ buffering in brain
    - Endocochlear potentials
    - K^+ secretion
  - Knockout
    - Spinal hypomyelination
    - Loss of endocochlear potentials & oligodendrocyte K^+ conductance
- KCNJ11 (Kir6.2)
  - Associates with sulfonylurea receptor (SUR1)
  - Controlled by G-proteins
  - ATP-sensitive
  - Expression: Ubiquitous
  - Function: Mediates glucose homeostasis; Glucose-stimulated insulin secretion
  - Diseases
    - Hyperinsulinemic hypoglycemia: Unregulated insulin secretion
    - May contribute to Type 2 diabetes: E23K polymorphism
    - Neonatal diabetes, transient or permanent
- KCNJ12 (Kir2.2)
  - Channels formed by homotetramers or associations with other Kir2
  - ATP sensitive
  - Role in action potential waveform and excitability of neurons & muscle
- KCNJ13 (Kir7.1)
  - Localization: GI; Neurons; Kidney; Retinal pigment epithelium
  - Mild inwardly rectifying K^+ current: Inverse dependence of conductance on $[K^+]_o$
  - Function: K^+ conductance of the Retinal pigment epithelium apical membrane
- KCNJ14 (Kir2.4)
  - Cranial nerve motoneurons in general somatic & special visceral motor cell columns
- KCNJ15 (Kir4.2)
  - Localization: Kidney
  - Forms heterodimer with KCNJ16
- KCNJ16 (Kir5.1)
  - Tissues: Brain, Kidney & Pancreas
  - Functional channels formed with: KCNJ15; PSD-95

- Associated with CO_2 chemoreception
- KCNJN1
  - Inhibitor of KCNJ12 (Kir2.2)
- Human ether-a-go-go (HERG; KCNH): Related to cyclic nucleotide-gated cation channels
  - KCNH1
    - Expressed at onset of human myoblast differentiation
  - KCNH2
    - **Channel** activation accelerated by K^+ **Channel** regulator 1
    - Diseases
      - Long-QT 2 syndrome
      - Short QT syndrome 1
  - KCNH3
    - Locations
      - Cerebral cortex: Layer II to layer VI; Cell bodies of neurons with pyramidal shapes
      - Hippocampus: CA1 & CA3 pyramidal cell body layers; Granule cell layers of dentate gyrus
    - Electrophysiology: Voltage-gated outward current with a fast inactivation component
  - KCNH4
    - Locations: Brain specific
      - Striatal regions: Putamen & caudate nucleus
      - Lower levels in cerebral cortex & hippocampus
    - Electrophysiology
      - Voltage-gated outward current
      - No fast inactivation component
  - KCNH5
    - Adult brain tissue
  - KCNH6 (HERG2)
    - Time constant for deactivation: Voltage dependent; Decreased with more negative potentials
    - Deactivation kinetics slower than KCNH7
  - KCNH7 (HERG3)
    - Time constant for deactivation: Voltage dependent; Decreased with more negative potentials
    - Fast deactivation kinetics
  - KCNH8
    - Locations: Forebrain; Testis
    - K^+ current at depolarizing voltages
      - Outward
      - Slowly activating
      - Noninactivating
      - Slowly deactivating
- KCNK family: 4 transmembrane domains; 2 pore (P) (tandem pore) domains;
  - General
    - "Leak" channels: Goldman-Hodgkin-Katz (GHK) outward rectification
  - KCNK1 (TWIK):
    - Weakly inward-rectifying current
    - Control of background K^+ membrane conductances
    - Expressed in CNS
  - KCNK2 (TREK):
    - Outward rectifying
    - Sensitive to extracellular K^+ & Na^+
    - Expressed in CNS

- Activated by Halothane
- KCNK3 (TASK)
  - Inhibited by extracellular acid: ? Role in cell response to extracellular pH
  - Activated by Halothane
- KCNK4 (TRAAK)
  - Expressed in neural tissues
  - Currents: K^+ selective, instantaneous, noninactivating, & outwardly rectifying
  - Potentiated by polyunsaturated fatty acids, e.g. arachidonic acid
- KCNK5 (TASK2)
  - Location: Renal
  - Inhibited by extracellular acid
- KCNK6 (TWIK2; TOSS): Many tissues; Eye ganglion cells & inner nuclear layer
- KCNK7 (TWIK-1-like)
  - Expressed in CNS
  - No **channel** activity when expressed alone
- KCNK8
  - Expressed in eye, lung, & stomach
  - No **channel** activity when expressed alone
- KCNK9 (TASK3 protein)
  - Expression: ? Selectively in cerebellum or Widely expressed
  - Oncogenic: Over-expressed in human carcinomas
  - Time-independent, noninactivating K^+-selective current
  - Current highly sensitive to changes in extracellular pH: Inhibited by extracellular acid
  - Blocked by barium, quinidine, and lidocaine
  - Subunits of heteromeric channels in orexin (hypothalamic) neurons that are sensitive to glucose
- KCNK10 (TREK2)
  - Rapidly activating & noninactivating outward rectifier K+ **channel** currents
  - Stimulation
    - Strongly by polyunsaturated fatty acids: Arachidonic acids
    - Cell membrane stretch
    - Intracellular acidification
    - Inhalational general anesthetics
    - Transiently activated by riluzole
- KCNK12 (THIK-2; Tandem pore domain Halothane Inhibited K^+ **channel**) PM
  - Expressed in brain & kidney
  - No functional current detected
  - Inhibited by Halothane
- KCNK13 (THIK-1)
  - Ubiquitous expression: High in olfactory, septal, hypothalamic & thalamic nuclei of brain
  - Weak inward rectification
  - Current enhanced by arachidonic acid
  - Current inhibited by halothane
- KCNK14
- KCNK15
  - Expression in heart, skeletal muscle, testis, thyroid gland, adrenal gland, salivary gland, pancreas
- KCNK16 (TALK-1)
  - **Channel** properties
    - K^+ currents: Outward rectifying; Lost by elevation of extracellular K^+
    - Activated at alkaline pH
    - Current sensitive to barium, quinine & volatile anesthetics: Inhibited by halothane
  - Distribution: Pancreas

- KCNK17 (TALK2; TASK4)
  - **Channel** properties
    - K^+ currents: Outward rectifying; Lost by elevation of extracellular K^+
    - Activated at alkaline pH
    - Current sensitive to barium ± quinine & volatile anesthetics
  - Distribution: Liver, lung, placenta, pancreas, small intestine, aorta

- KCNM: Ca^{++} sensitive; Large conductance channels (MaxiK)
  - General
    - Respond to increased intracellular Ca^{++} ion concentrations
    - α-subunit: Pore forming
    - β-subunit: Modulatory
    - Sensitive to peptide toxins: Charybdotoxin, Iberiotoxin; Bind to β-subunit
    - Functions
      - Play a role in leukocyte-induced microbial death
      - Translate Ca^{++} signals to vasoregulation
  - KCNMA1: Ca^{++} activated; Large conductance
    - Mediates fast, Ca^{++}-activated K^+ current
    - 17-β-estradiol binds to β subunit
    - May play role in cochlear frequency selectivity
    - Fetal skeletal muscle
    - Disease: Generalized epilepsy + Paroxysmal dyskinesia
    - Null mice: Ataxia & Vascular (smooth muscle) dysfunction
  - KCNMB1
    - Smooth muscle, Skeletal muscle (Fetal), Brain (Hippocampus, Corpus calosum)
  - KCNMB2: Ca^{++} activated; Large conductance
    - Subunit induces fast inactivating currents that can be increased by voltage & intracellular Ca^{++}
  - KCNMB3
  - KCNMB4
- KCNN: **Calcium**-activated, Small/Intermediate conductance
  - KCNN1 (SK1)
    - Brain, Heart
    - Small conductance, Ca^{++} activated
    - Apamin sensitive
  - KCNN2 (SK2)
    - Brain, Adrenal gland, Retinal ganglion cells & neurons
    - Apamin, Scyllatoxin & Tubocurarine sensitive
    - Charybdotoxin insensitive
  - KCNN3 (SK3)
    - Small conductance, Ca^{++} activated
    - Intermediate apamin sensitivity
    - Contains 2 CAG repeat sequences:
      - Polymorphisms
      - Long CAG sequences: Not causative but ? Associated with sporadic ataxia[13]
    - Brain, Heart, Skeletal muscle (Embryonic), Liver
  - KCNN4 (SK4)
    - T-lymphocytes; Colon, Smooth muscles, RBCs, Neurons
    - Intermediate conductance
    - Ca^{++} activated
    - Blocking agents: Clotrimazole; Charybdotoxin
    - Major pathway for cell shrinkage via KCl and water loss in sickle cell disease
- KCNT family: Intermediate-conductance **calcium**-activated

        - General
            - Activated by intracellular Na^+ & Cl^-
            - Inhibited by intracellular ATP
        - KCNT1 (Slack)
            - Expression
                - Moderate to high in all tissues
                - Highest in liver & brain
                - Lowest in skeletal muscle
            - Interacts with Slo subunits
        - KCNT2 (Slick)
    - SUR (High-affinity sulfonylurea receptor)
        - SUR1 (ABCC8): Pancreatic islets
        - SUR2 (ABCC9)
            - 2A: Heart
            - 2B: Brain, Liver, Skeletal & Smooth muscle, Bladder
    - Plasmolipin
        - Brain (myelin) & Kidney
        - Forms K^+ specific, voltage-dependent channels when added to lipid bilayers

- **Disorders of K^+ Channels**

- Toxins[1]
    - Organic: 4-aminopyridine; Tetraethyl-ammonium
    - Polypeptide
        - Agitoxin-2
        - Apamin
        - Charybdotoxin
        - Dendrotoxin
        - Tityus toxin K-α
        - Tarantula toxins
            - Voltage sensor toxin 1 (VSTX1; Tarantula venom)
                - Inhibits KvAP voltage dependent **channel**: Partitions in lipid membrane, then binds to receptor[20]
            - Hanatoxin 1: Binds to Kv2.1 & Kv4.2; Alters gating energetics
            - Hanatoxin 2: Binds to Kv2.1; Blocks K^+ currents
    - Barium
    - Aldosterone-like: Licorice (Glycyrrhizic acid); Carbenoxolone (Glycyrrhetinic acid)
    - Volatile substances: Toluene
    - Ethanol
    - Cottonseed oil (with low dietary K+)
    - Bergamot oil (Bergapten; 5-methoxypsoralen): Earl Grey tea
- Immune
    - Neuromyotonia
    - Cramp-fasciculation syndrome
    - Morvan's fibrillary chorea
    - Limbic encephalitis
- Hereditary
    - Hypokalemic periodic paralysis: KCNE3
    - Andersen syndrome: KCNJ2 (Kir2.1)
    - Bartter syndrome (Hypokalemic alkalosis with hypercalciuria), type 2
        - Inward rectifing K^+ **channel**, Subfamily J, Member 1 (KCNJ1)
        - Also caused by mutations in $Na^+/K^+/Cl^-$ transporter-2 (SLC12A1) and Cl^- **channel** (CLC-Kb)

- Cardiac: Long-QT Syndromes
  - KVLQT (LQT1 syndrome): Voltage gated K^+ **channel** (KCNQ1)
    - Jervell & Lange-Nielsen Syndrome: Recessive
    - Romano-Ward Syndrome: Dominant
  - HERG (LQT2 syndrome): Inward rectifying $K^{\pm}$ **channel** (KCNH2)
  - LQT4: Chromosome 4q25-q27; ? gene
  - Jervell & Lange-Nielsen Syndrome: Recessive
    - 2 genetic causes
      - K^+ Voltage gated **channel**, ISK-related subfamily, Member 1 (KCNE1)
      - KCNQ1 (KCNA8; KVLQT1) $K^{\pm}$ **channel**
    - Long-QT syndrome & Congenital hearing loss
    - Mechanism of arrhythmia
      - Accelerate **channel** incativation
      - Delays myocardial repolarization
  - Long QT syndrome 5: KCNE1
  - Long QT syndrome 6: KCNE2 (minK related peptide 1)
    - Ventricular fibrillation; Clarithromycin-induced arrhythmia
- Cardiac: Other
  - Atrial fibrillation, Dominant: KCNQ1
  - Short QT syndrome 1: KCNH2
  - Short QT syndrome 2: KCNQ1
  - Short QT syndrome 3: KCNJ2
- Neural
  - Episodic Ataxia / Myokymia Syndrome: KCNA1 (Voltage gated K^+ **channel**)
  - SCA 13: KCNC3 (Kv3.3)
  - Myokymia & Benign neonatal epilepsy: KCNQ2
  - Benign neonatal epilepsy: KCNQ2: & KCNQ3
    - Mutations cause reductions in size of K^+ currents
  - Generalized epilepsy + Paroxysmal dyskinesia: KCNMA1
  - ?? Paroxysmal Choreoathetosis/Spasticity
- Hyperinsulinemic hypoglycemia of infancy: Familial persistent
  - Subunit of ATP-sensitive pancreatic β-cell K^+ **channel** (ABCC8)
    - High-affinity sulfonylurea receptor (SUR1)
  - Inwardly rectifying K^+ **channel**: BIR subunit (KCNJ11); Pancreatic β-cell
- Non-syndromic hearing loss, Dominant: KCNQ4
- Cone dystrophy with supernormal rod electroretinogram: KCNV2 (Kv11.1)
- Weaver mouse: G-protein coupled, inward rectifing K^+ **channel** (KCNJ6)
  - Human homologue gene at Chromosome 21q22.1

HYPOMAGNESEMIA

- Clinical
  - Seizures
  - Tetany
  - Paresthesias
  - Weakness
- Genetic syndromes
  - Primary hypomagnesemia
    - Claudin 18; Chromosome 3q; Recessive

- Hypomagnesemia with secondary hypocalcemia
  - Chromosome 9q12-q22.2; Recessive
- Magnesium & **Potassium** depletion (Gitelman syndrome)
  - Na-Cl cotransporter; Chromosome 16q13; Recessive
- Hypomagnesemia 2, Renal (HOMG2)
  - Chromosome 11q23; Recessive

ANION CHANNELS, EXCHANGERS & TRANSPORTERS

- Anion exchange proteins:
  - SLC4A1 (AE1): Erythrocyte band 3 protein
    - Major integral glycoprotein in erythrocyte membrane
    - Polymorphisms determine Diego blood group
    - Diseases: Spherocytosis; Ovalocytosis; Renal tubular acidosis; Hypokalemic periodic paralysis
  - Other
    - SLC4A2: Anion exchanger; ? Choroid plexus, GI & Other
    - SLC4A3: Anion exchanger; Cardiac & Brain
    - SLC4A4: Na Bicarbonate cotransporter; Renal; Renal tubular acidosis, glaucoma, cataracts, & band keratopathy
    - SLC4A5: Na Bicarbonate cotransporter; Pancreas
    - SLC4A6: Na Bicarbonate cotransporter; Retina
    - SLC17A5 (Sialin): Salla syndrome (Sialic acid storage)
    - SLC26A3: Down-regulated in adenoma (DRA)
      - ? Sulfate transporter
      - Congenital chloride diarrhea
    - SLC26A4: Transporter of Chloride & Iodide
      - Non-syndromic deafness, congenital (DFNB4)
      - Pendred syndrome
      - Enlarged vestibular aqueduct syndrome
- Voltage dependent anion selective **channel** proteins (VDAC)
  - Location: Outer mitochondrial membrane ± plasma membrane
  - Functions
    - Channels for small hydrophilic molecules
    - Translocation of adenine nucleotides through outer mitochondrial membrane
    - BCL2 proteins bind to VDAC: Regulate mitochondrial membrane potential & release of cytochrome c during apoptosis
    - Mitochondrial binding site for hexokinase (see HK1; 142600) and glycerol kinase
  - VDAC1;
    - Pathway for movement of adenine nucleotides through outer mitochondrial membrane
    - Mitochondrial binding site for hexokinase and glycerol kinase
  - VDAC2
    - Open conformation: At low or zero membrane potential; Weak anion selectivity
    - Closed conformation: At potentials above 30-40 mV; Cation-selective
  - VDAC3
    - High expression in testis
    - Null mice
      - Sperm motility: Reduced
      - Muscle: Mitochondria abnormally shaped, Respiratory chain complex activity reduced
  - VDAC4
- Organic anion transporter (OATP)
  - Na^+-independent transport of organic anions, e.g. bile acids

- Canalicular multispecific organic anion transporter (cMOAT)
  - Dubin-Johnson Syndrome
- Sulfate anion transporter

CATION CHANNELS: CYCLIC NUCLEOTIDE-GATED

- CNG channels
  - α1 subunit (CNGA1)
    - Localization: Rod photoreceptors
    - Integral membrane protein
      - Mediates visual signal transduction
      - Cyclic GMP is 2nd messenger: Activates cation **channel** → Rod photoreceptor depolarization
      - Polymerizes with CNGB1
      - Stimulation: Darkness opens channels to Na^+ & Depolarizes photoreceptors
      - Inhibition: Light activates cGMP causing **channel** closure & Hyperpolarizes photoreceptors
    - Disease: Retinitis pigmentosa
  - α2 subunit (CNGA2): Olfactory
    - Activated by 3 molecules of cATP
    - **Channel** ions: Na^+ & Ca^{++}
  - α3 subunit (CNGA3)
    - Localization: Testis; Kidney; Heart; Eye
    - Disease: Rod monochromacy (Total color blindness; Achromatopsia 2)
  - α4 subunit (CNGA4)
    - Olfactory signaling: Mediates negative feedback; Allows rapid adaptation
  - β1 subunit (CNGB1): Retina with CNGA1
  - β3 subunit (CNGB3): Achromatopsia 3 (Pingelapese blindness)
  - Brain CNG 1 & 2: Voltage gated K^+ channels
- Ca^{++} transporting ATPase
- ATP-gated Cation **Channel** (ACC) Family (P2X receptors)
- Cu^{++} transporting ATPase 7
  - Wilson's: β polypeptide
  - Menkes: α polypeptide
  - Occipital horn syndrome: α polypeptide
- K^+/H^+ ATPase: B_{12} deficiency
- Hyperpolarization-activated cyclic nucleotide-gated K^+ channels (HCN)

PROTON-GATED ION CHANNELS: Neural

- General
  - Two-transmembrane-domain proteins
  - Related to putative mechanosensory DEG/ENaC channels
  - Gated by reductions in extracellular pH
  - Most subtypes expressed in DRG: ASIC1b & ASIC3 have preferential expression in sensory ganglia
- Types
  - Dorsal root acidic sensing **channel** (DRASIC; ASIC-3):
    - Form hetermultimeric channels

        - Location
            - DRG neurons: Large-diameter mechanoreceptors; Unmyelinated small-diameter peptidergic nociceptors
            - Sensory nerve terminals: Meissner corpuscles lanceolate fibers; Rapidly adapting low-threshold mechanoreceptors
            - Free nerve endings: ? Nociceptors
        - Low pH opens **channel** to Na^+ & Ca^{++}
        - Curent: Biphasic; Rapidly inactivating & Sustained components
        - Inhibitor: Amiloride
        - Functions: Related to
            - Stimuli: Cutaneous touch; Acid
            - Role for ASIC3 in tonic inhibition of high-intensity pain signals
        - ASIC3-deficient mouse
            - Reduced sensitivity of some mechanoreceptors to noxious pinch
            - Enhanced sensitivity to light touch
            - Enhanced behavioral responses to high-intensity nociceptive stimuli
    - Acidic sensing ion **channel** (ASIC-1)
        - 2 variants
            - Alpha (ASIC-α): Expressed widely in brain
            - Beta (ASIC-β): Expressed only on sensory neurons
        - Inhibitor: Amiloride
        - Ion permeability: $Na^+ > Ca^{++} > K^+$
        - Activation: Transient (Rapidly inactivating); By rapid extracellular acidification
        - Disease
            - Focal ischemia or acidosis: May play a role in cell injury
            - ASIC1A & H^+-gated currents: May contribute to fear & anxiety disorders
    - Mammalian degenerin homologue (MDEG-1; ACCN1; BNC1) (ASIC-2): Na^+ **channel**
        - Inhibitor: Amiloride
        - Excited by: Hair movement; Acid, ASIC2b with ASIC-3
        - Physiologic function
            - Role in: Mechanically stimulated graded potential in axonal receptors
            - Nociception: Acid-induced cardiac pain
            - Not related to detection of noxious mechanical stimuli
        - Location
            - Palisades of lanceolate nerve endings around hair follicles
            - Dorsal root ganglion cells: Large & Small
        - ASIC-2 deficient mice
            - Rapidly adapting mechanoreceptors: Reduced sensitivity to hair movement
            - Some reduced sensitivity in response of slowly adapting mechanoceptors
    - ASIC-4 (SPASIC)
        - Expressed in pituitary & brain
    - Capsaicin receptor (VR1)

Na-K-Cl CO-TRANSPORTERS (Solute carrier family (SLC) 12)

- General
    - Integral membrane proteins
    - Mediate coupled transport of Na^+, K^+, & Cl^- across plasma membrane
    - KCC family members: **Potassium**-Chloride cotransporters
- Types

- SLC12A1 : Renal
  - Mediates active reabsorption of NaCl
  - Location: Thick ascending limb of the loop of Henle
  - Site of action of diuretics: Furosemide; Bumetanide
  - Disease: Bartter syndrome (Antenatal)
- SLC12A2
  - Expressed in many tissues: Secretory epithelia
  - Mediates active Cl^- secretion
  - Mouse mutation
    - Deafness; Shaker/waltzer behavior, indicative of inner-ear defects
    - Endolymph secretion: Reduced
- SLC12A3 : Renal
  - Distal convoluted tubule: Principal mediator of Na^+ & Cl^- in this segment
  - Target of thiazide diuretics
  - Disease: Bartter syndrome (Gitelman variant)
- SLC12A4 (KCC1) : Early erythroid maturation
- SLC12A5 (KCC2)
  - Chloride extruder in brain
  - Promotes fast hyperpolarizing postsynaptic inhibition
  - Knockout mouse: Early death; Abnormal axon spontaneous activity
- SLC12A6 (KCC3)
  - Tissues: Vascular endothelial; Brain; Heart; Skeletal muscle; Kidney
  - Increased activity with cell swelling
  - Disease: Andermann syndrome (HMSN & Agenesis of Corpus Callosum)
- SLC12A7 (KCC4) :
  - Highest expression in kidney, heart, lung, and liver
  - Knockout mice
    - Deafness: Outer hair cells of basal turns of the cochlea lost
    - Renal tubular acidosis: Other causes are hydrogen ATPase & AE1 (SLC4A1) anion exchanger
  - Function: **Potassium** recycling into Deiters cells after exit from hair cells

---

Stretch-activated non-selective cation channels (SA channels)

- Mechanism: Mechanically-gated channels
- Locations
  - Ear
  - Muscle spindles
  - Vascular endothelial cells
  - Neurosensory epithelia
- Types

TRANSIENT RECEPTOR POTENTIAL (TRP) ION CHANNELS

General Features

- Structure

    - Subunits: Contain 6 membrane spanning domains
    - Similarity
        - Voltage gated K+ (K_v)
        - Cyclic nucleotide gated (HCN & CNG)
        - Polycystic kidney disease proteins
    - Form tetramers
    - Pore lined by transmembrane domains 5 & 6
- Location: Plasma membrane
- Functions
    - Non-selective cation **channel**
    - Act to shift membrane potential to 0 mV
    - Depolarization from resting membrane potentials
    - Allow Ca^{++} influx in non-excitable cells
    - Some are temperature sensitive
- **Channel** opening: Linked to activation of 2nd messenger systems
    - Activation of phospholipase C
    - Generation of Inositol-1,4,5-triphosphate ($Ins(1,4,5)P_3$)
    - Opening of $Ins(1,4,5)P_3$ receptor
    - Response to depletion of intracellular **calcium** pools (Capacitative **calcium** entry)
- Some TRP play a role in phototransduction

TRP families[12]

- TRPA receptors
    - TRPA1 (ANKTM1)
        - Stimuli
            - Thermal stimulus: < 17 °C; Noxious cold
            - Mechanoreceptors in hair cells
        - Pharmacologic stimuli: May evoke burning sensation
            - Icilin
            - Pungent natural compounds in
                - Cinnamon oil (cinnamaldehyde)
                - Wintergreeen oil (methyl salicylate)
                - Clove oil (eugenol)
                - Mustard oil (allyl isothyocianate)
                - Ginger (gingerol)
                - Garlic (alllicin)
                - Wasabi (allyl isothiocyanate)
        - **Channel** properties: Non-selective cation currents
        - Cell localization
            - Dorsal root ganglia. Expressed in some cells that also express TRPV1 (heat-gated **channel**)
                - May be up-regulated by NGF via p38 MAPK pathway
            - Hair cells
- TRPC receptors (STrpC)
    - TRPC1 : Expression widespread; Activated by diacylglycerol (DAG) & Intracellular Ca^{++} depletion
    - TRPC2 : Vomeronasal organ, Testes, Heart, Brain, Sperm; ? Pseudogene in humans
    - TRPC3 : Brain, Placenta, Heart, Muscle; Activated by DAG & $InsP_3R$; Inward & Outward rectifying
    - TRPC4 : Brain cortex, Testes, Placenta, Adrenal, Endothelium; Receptor operated
    - TRPC5 : Brain; Receptor operated
    - TRPC6
        - Tissues: Lung, Brain, Muscle (Smooth)
        - Activated by DAG

        - Inward & Outward rectifying
        - Interacts with podocin & nephrin
        - Disease: Focal segmental glomerulosclerosis
    - TRPC7: Lung, Brain, Muscle (Smooth), Heart, Eye; Activated by DAG; Inward & Outward rectifying
- TRPV receptors
    - General: TRPV family contains many heat-sensitive channels
    - TRPV1: Vanilloid receptor (VR1); Capsaicin receptor
        - Location
            - Brain
            - Spinal cord: Laminae II & III of dorsal horn
            - Peripheral sensory neurons
                - Location: DRG; Trigeminal; Nodose
                - Size: Small to medium diameter
                - Peptide & Non-peptide releasing
            - Other: Urinary bladder epithelium, Smooth muscle, Epidermal keratinocytes
        - Subcellular location: Plasma membrane
        - Physiology
            - Outwardly rectifying
            - Cation **channel**: Relatively selective for Ca^{++}
        - Activated by
            - Capsaicin: Sensory ganglion cells & axons
            - Resiniferatoxin (RTX): Highly potent analog
            - Anandamide: Cannabinoid receptor ligand; Sensitized to anandamide by protein kinase C
            - Temperature
                - Heat to noxious range: 45 °C (Lower after sensitization
                - Steep temperature dependance
            - Low pH (Acid)
                - 2 effects of protons
                    - Activation of VR1 at room temperature: With extracellular pH < 6
                        - Currents resemble sustained component of proton-evoked responses in sensory neurons
                    - Potentiate responses of VR1 to capsaicin or heat
                        - Concentration range (pH 6–8) matches local acidosis associated with tissue injury
                - More mediation of sustained than transient responses
        - Inhibitors
            - Capsazepine
            - Ruthenium red
            - Phosphatidylinositol (4,5)-bisphosphate
        - Release of VR1 from inhibitory control: Bradykinin & Nerve growth factor
        - Functions
            - Nociception
                - Heat, Acid or Stretch induced
                - Activation effects
                    - Releases neuropeptides (substance P) from nerve terminals
                    - Causes burning pain
            - Inflammation
            - Hypothermia
            - Integrates effects of noxious heat, low pH & vanilloid ligands on sensory neurons
        - Experimental modification
            - VR1 knockout mouse
                - Severely deficient in moderate heat-evoked responses
                - Few heat-sensitive C axons
                - Reduced pain behavior at high temperatures (> 50°C)

        - No increased sensitivity to heat after tissue injury
      - Anti-VR1 serum: Ameliorates thermal allodynia and hyperalgesia in diabetic mice
  - TRPV2 : Vanilloid receptor-related (VRL-1)
    - Location: Brain; Spinal cord; Spleen; Lung; Peripheral sensory neurons
    - Physiology
      - Outwardly rectifying
      - Ions: $Ca^{++} > Na^{+}$ permeability
      - Inhibition by ruthenium red
    - Noxious heat sensation: Activated at 53 °C
  - TRPV3 : VRL-3
    - Location: Keratinocytes
    - Activation
      - Warm temperatures (25 to 40 °C
      - High response at noxious hot temperatures
  - TRPV4 : VRL-2
    - Location: Brain; Liver; Kidney; Fat; Heart; Testes; Salivary gland; Trachea
    - Outward rectifying
    - Activation
      - Reduced osmolarity
        - Mediates sensitivity of nociceptive dorsal root ganglion neurons to hypoosmotic challenges
      - Mechanosensitive: ? via 2nd messenger
      - Warm temperatures ($25°C_T$ 40°C)
    - TRPV4-null mice: Reduced sensitivity of tail to pressure & acidic nociception
    - AQP5 abundance in hypotonic conditions: Can be regulated by TRPV4
  - TRPV5 : ECAC-1
    - Location: Intestine; Kidney; Placenta
    - Inward rectification
    - Ca^{++} selective
    - Conductance increases in absence of divalent catiions
    - Associated with 1,25 dihydroxyvitamin D3-dependent calbindin-D_{28K}
    - ? Role in Vitamin D responsive Ca^{++} uptake
  - TRPV6 : ECAC-2
    - Location: Widespread
    - Ca^{++} selective
    - Inward rectification
    - Passes most current at hyperpolarized potentials
    - Activated by Ins(1,4,5)P_3 & thapsigargin-mediated store depletion
- TRPM (Long TRP, Melastatin)
  - TRPM1
    - Eye (Melanocytes)
    - Down-regulation prognostic marker for metastasis
  - TRPM2
    - Brain (Fetal & Adult), Placenta
    - ADP-ribose regulation
    - Non-selective **channel**
  - TRPM3
  - TRPM4 :
    - Highest levels: Heart; Prostate; Colon; Kidney (In fetus)
    - Activated by intracellular Ca^{++}
    - Conducts monovalent cations: Na^{+} & K^{+}
    - Modulates membrane potential

- TRPM5
  - Strong outward rectification
  - Nonselective among monovalent cations
  - Not permeable to divalent cations
  - Regulated by
    - Intracellular Ca^{++}: Activates & Desensitizes
    - PIP2: Reverses desensitization
  - Widely expressed
  - Taste transduction **channel**
  - Associated with Beckwith-Wiedemann syndrome
- TRPM6
  - Mutations in hypomagnesemia with secondary hypocalcemia (HSH)
- TRPM7 (TRP-PLIK)
  - Kidney, Heart, Liver, Spleen, Lung, Brain
  - Regulated by activity of carboxy terminal kinase
  - Non-selective, whole cell current
- TRPM8
  - Voltage-dependent gating cold-sensitive **channel**
    - Activation
      - Initial activation: Cooling to 28 °C
      - Activity increases as temperature diminishes: Increased probability of **channel** opening
      - Saturation: 10 °C
    - Menthol receptor on axons
    - May also be activated by Icilin, eucalyptol & WS-3
  - Nonselective outwardly rectifying **channel**
  - Prostate, especially neoplasms
  - Upregulated by NGF

- TRPN
  - General features
    - Contain ankyrin repeats in N-terminals
  - Painless
    - Stimulus: Heating (Noxious) to > 41°C
    - Present in multidendritic neurons: CNS & PNS
  - no-mechanoreceptor-potential C (nompC)
    - Stimulus: Mechanical (Hair)
  - Ankyrin-like protein with transmembrane domains 1 (ANKTM1)
    - Cold-activated **channel**: < 17 °C; Noxious
    - Location: Nociceptive cold-sensitive sensory neurons
      - Coexpressed with the capsaicin/heat receptor
      - Sensory neurons respond to capsaicin but not to menthol
  - Pyrexia
    - Gene encodes 2 proteins: PYX-PA & PYX-PB
    - Sequence homologies to other TRP proteins: ANKTM1; Painless
    - Subunits form heteromeric channels
    - Expressed along dendrites of a subset of peripheral nervous system neurons
    - Opened by temperatures above 40 °C
    - More permeable to K^+ than to Na^+
    - Protects against high temperature stress
- PKD (Polycystin) family
  - PKD Function
    - PKD1 & PKD 2 interact to produce Ca^{++}-permeable nonselective cation currents
    - Ion **channel**: Contributes to fluid-flow sensation by primary cilium in renal epithelium
      - Activated by bending of the apical cilium in some epithelia

        - Senses fluid flow parallel to the epithelial surface.
    - PKD1 : Polycystic kidney disease, Dominant
    - PKD2 : Polycystic kidney disease, Dominant
    - Mucolipin 1 (MCOLN1)
        - Cationic **channel**
        - Functions
            - Endocytic pathway
            - Control of membrane trafficking of proteins and lipids
            - ? Ca^{++} transport regulating lysosomal exocytosis
        - Mucolipidosis IV
    - Mucolipin 2 (MCOLN2)
    - Mucolipin 3 (MCOLN3)
        - Mouse disorder: varitint-waddler (Va) with tricolor & hearing loss

---

GAP JUNCTIONS[23]


Gap junction

- External link: Expasy
- General
    - Definition: Clusters of intercellular channels connecting cytoplasms of two cells
    - Functions: Coupling
        - Metabolic: Flow of metabolites between cells
        - Electrical: Flow of ions between cells
            - Signaling between neurons
            - Especially prominent in developing nervous system
            - May affect the dynamics of brain circuits: Synchronous firing of coupled neurons
        - Patterns
            - Symmetric
                - Non-rectifying
                - ± Voltage-sensitive
                - Behavior independent of hyperpolarized side
            - Asymmetric
                - May depend on: Type of **channel**; Properties of coupled cells
                - May be rectifying
    - Formed by: Connexins (Vertebrates); Innexins (Invertebrates)
    - Structure
        - Each intercellular **channel** of a cluster comprises one multimeric hemichannel from each cell
        - Each species contains a family of gap-junction monomers
        - Each cell usually expresses more than one type of monomer
- Connexins
    - General: Connexin properties & association with gap junctions
        - Multi-gene family
            - Number: 21 in humans
            - Sequence homology: 40%
        - Molecular structure of connexins
            - Membrane-spanning domains: Four; α-helical
            - Extracellular: 2 loops
            - Cytoplasmic: Carboxy and amino terminal sequences; 1 Loop
        - Connexon
            - Formed by a hexameric array of connexins
            - May be homomeric or heteromeric
        - Gap junction structure

- Composition
  - Pair of connexons joined end-to-end in extracellular space: Forms tight seal
  - Connexons may be same (Homotypic) or different (Heterotypic)
- Forms a hydrophilic intercellular membrane **channel**
- Associated with 2 to 3 nm gap between neighboring cell membranes

- Gap junction **channel** function
  - Allows diffusion of low molecular weight molecules (< 1kDa) between neighboring cells
  - Molecule types: Ions; Amino acids; Nucleotides; Cyclic AMP; Glucose-6-phosphate; Tetrahydrofolic acid
  - Gating: Controlled by multiple factors
    - **Calcium** concentration
      - Closed by high concentrations: Mediated by calmodulin
    - pH: Closed at acid pH
    - Transjunctional membrane potential: Closed by large transjunctional voltages
    - Protein phosphorylation
- Gap junctions: Associated structures
  - Cadherin-based adherens junctions
- Disease syndromes caused by connexin mutations
  - Deafness
  - Polyneuropathy
  - Skin disorders
  - Cataracts

- Types of connexins
  - Connexin 26 (GJB2; CXB2)
    - Diseases
      - Non-syndromic deafness - Recessive & Dominant (DFNA3)
      - Vohwinkel syndrome
      - Heterozygosity: Exacerbating factor for A1555G mitochondrial deafness (Aminoglycoside)
  - Connexin 29 (GJE1)
    - Locations
      - Tissues: Brain, Spinal cord, Peripheral nerve
      - Subcellular: Schwann cell membrane near Kv1.2 channels on axon
  - Connexin 30 (GJB6)
    - Diseases
      - Deafness, Autosomal dominant, Nonsyndromic Sensorineural 3 (DFNA3)
      - Ectodermal dysplasia 2, Hidrotic (Clouston syndrome) [21]
        - Clinical: Strabismus, Mental deficiency, Finger clubbing, Palmar hyperkeratosis
        - Mutant protein
          - Forms functional hemichannels at cell surface
          - Generates leakage of ATP into extracellular space
  - Connexin 30.3 (GJB4)
    - Disease: Erythrokeratodermia variabilis
  - Connexin 31 (GJB3)
    - Diseases
      - Erythrokeratodermia variabilis
      - Bilateral high-frequency hearing loss (AD)
      - Hearing loss & polyneuropathy
  - Connexin 32 (GJB1; CXB1)
    - Disease: CMT-X
  - Connexin 36 (GJA9): Formation of functional gap junctions in neocortex interneurons
  - Connexin 40 (GJA5): Cardiac; Intercalated disk regions of left ventricle
  - Connexin 43 (CXA1; GJA1)
    - Tissue: Heart

- Oculodentodigital Dysplasia
- Mouse knockout: Cardiac right ventricular outflow obstruction

- Connexin 46 (GJA3)
  - Disease
    - Cataract, Zonular Pulverulent, 3
    - Animal model: Nuclear cataracts with proteolysis of crystallins
- Connexin 46.6 (GJA12)
  - Diseases: Pelizaeus-Merzbacher-like syndrome
- Connexin 50 (GJA8)
  - Diseases: Cataract, Zonular pulverulent 1
- Other connexins
  - 31.1 (GJB5): Skin
  - 31.9 (GJC1): Gated by cytoplasmic acidification or halothane
  - 33 (GJA6): Testis
  - 37 (GJA4): Multiple organs
  - 45 (GJA7)

- Other cell junctions involved in intercellular adhesion include
  - Desmosomes
    - Large bundles: Anchor epithelial cells together
    - Proteins: Desmocollins; Desmogleins; Plakoglobins; Desmoplakins
    - Diseases: Pemphigus; Congenital muscular dystrophy; Naxos disease
  - Tight junctions
    - Leave little space (< 1 nm) between two plasma membranes
    - Functions
      - Selectively modulate paracellular permeability between extracellular compartments
      - Act as boundary between apical & basolateral plasma membrane: Maintain epithelial cell polarity
    - Proteins: Cingulin; Zo-1, -2 & -3; Claudins; Occludin, JAM, Symplekin, 7H6 antigen
    - Diseases
      - Claudin-11: In oligodendrocytes; Mouse knockout ? CNS myelin abnormalities
      - Claudin-14: Deafness, Autosomal Recessive (DFNB29)
      - Claudin-16: Primary Hypomagnesemia

ION CHANNEL-BINDING PROTEINS: INTRACELLULAR

Ion channel	Binding protein	Mechanism & Effect
$K^{\pm}$ channel, Voltage-gated Shaker type	Chapsyns*: PSD-95; SAP97; Chapsyn-110; Sap102; Dlg	Binding via PDZ** domains 1st & 2nd on PSD-95 Post-synaptic densities in CNS
NMDA receptor NR2 subunit		
NMDA receptor NR1 subunit	α-actinin	Actin binding protein Concentrated in dendritic spines
Glycine receptor (GlyR)	Gephyrin	Binds to β intracellular loop of GlyR & tubulin
AChR: Nicotinic	Rapsyn/43K	Neuromuscular junction localization
$Na^{\pm}$ channel Voltage-gated	Ankyrin G	Node of Ranvier localization

AMPA receptor GluR2 subunit	Glutamate receptor interacting protein (GRIP)	Binding via PDZ domain Couples receptor to cytoskeletal & signaling molecules
Glutamate receptor Metabotropic Subunits: mGluR1a & mGluR5	Homer	Binding via PDZ-like domain Expression ↑ by synaptic activity

* Belong to Membrane Associated Guanylate Kinase (MAGUK) family
Chapsyn = **Channel** associated protein of synapse
** PDZ domains: Homologous 90 amino acid sequence repeats; Bind other proteins

---

ACETYLCHOLINE RECEPTORS: Disorders

- Muscle
  - Myasthenia Gravis
    - Autoimmune: IgG vs α1 subunit
    - Hereditary
      - α-subunit
      - β-subunit
      - ε-subunit
      - δ-subunit
      - γ-subunit
- Neuronal
  - Immune neuropathies: Isaac's; Subacute autonomic
    - IgG antibody vs α3 subunit
    - Paraneoplastic syndrome: Associated with small cell lung carcinoma
  - Epilepsy
    - Nocturnal frontal lobe, Type 1
      - Neural nicotinic, α4 subunit; Chromosome 20q13.2-q13.3; Dominant
    - Nocturnal frontal lobe, Type 3
      - Neural nicotinic, β2 subunit (CHRNB2); Chromosome 1p21; Dominant
  - Schizophrenia: Attention disorder
    - Lack of inhibition of P50 response to auditory stimulus
    - Linked to dinucleotide polymorphism at 15q13-q14: Site of α-7-nicotinic receptor
  - Mouse knockouts
    - Lethal: ε-AChR subunit loss
    - CNS neuronal loss with subunit knockout
      - Neural nicotinic, β2 subunit of AChR (CHRNB2)
        - Defects localized in CA1 and CA3 fields in hippocampus & neocortex
      - α7 subunit: Minimal phenotype
      - α9 subunit: Altered innervation of cochlear hair cells
    - Autonomic dysfunction
      - Knockouts of neural nicotinic AChR subunits
        - α3: Bladder enlargement; Dilated, unresponsive pupils
        - β2
          - Nicotine-elicited anti-nociception: Reduced
          - Neurons in hippocampus & neocortex: Reduced
        - α4
          - Nicotine-elicited anti-nociception: Reduced
- Muscarinic
  - IgG vs M_3-muscarinic AChRs: Occur in both 1° & 2° Sjögren's

- Toxins
  - Nicotinic agonists: Nicotine; Anatoxin A
  - Nicotinic antagonists
    - Peptides: α-snake toxins; α-conotoxins
    - Other: d-tubocurarine; Histrionicotoxin; Lophotoxin; Epibatidine
  - Muscarinic agonists: Muscarine; Arecoline; Pilocarpine; Green mamba snake
  - Muscarinic antagonists: Scopolamine; Atropine

GLYCINE RECEPTORS

- Hyperekplexia (Startle disease)
  - Glycine receptor α-1 subunit (strychnine binding); Chromosome 5q33-q35; Dominant or Recessive
    - Same mutation in *Spasmodic* mouse
  - β subunit; Chromosome 4q31.3; Sporadic or Recessive
    - Also: *Spastic* mouse

- Toxins
  - Picrotoxin: Non-competitive antagonist of glycine-activated Cl^- **channel**
  - Strychnine: Competitive antagonist of glycine-gated Cl^- **channel**

GLUTAMATE RECEPTORS

- Metabotropic glutamate receptor R1 (mGluR1): Paraneoplastic cerebellar degeneration
- Metabotropic glutamate receptor R1 (mGluR3): Rasmussen's encephalitis

---

DOPAMINE RECEPTORS

- D4 subtype: Autonomic syndrome

Long QT Syndromes[16]

- Cardiovascular disorder with tachyarrhythmias: Prolonged ventricular repolarization
  - Ventricular fibrillation
  - Torsade de pointes
    - Fibrillation with waxing and waning
    - Due to changing axis of depolarization
- General: Molecular features
  - All LQT syndromes caused by K^+ **channel** disorders except LQT3
  - Mechanisms: Current carried by defective **potassium** channels is impaired by reduced gating or modified **channel** kinetics
- Epidemiology
  - Carriers: 1 in 10 000 persons
  - Congenital long QT syndrome causes 3000 to 4000 sudden deaths in children & young adults per year in US
  - Onset: 50% by 12 years; 90% by 40 years

- Clinical syndromes
  - Autosomal-dominant (Romano–Ward syndrome): Pure cardiac phenotype
  - Autosomal-recessive (Jervell and Lange–Nielsen syndrome): Association with congenital neuronal deafness
  - Acquired long QT syndrome: Due to electrolyte disturbances or drug therapy
- Risk factors for syncope or sudden cardiac death
  - Congenital deafness
  - History of syncope
  - Female: Cardiac events more common generally & during pregnancy
  - Males: Risk higher in childhood
  - Documented torsade de pointes or ventricular fibrillation
  - Age at first episode
  - Duration of the corrected QT interval (QTc)
- Clinical features
  - Syncope
  - Seizures
  - Sudden death
  - Treatment: β-blockers may reduce risk of cardiac events, especially LQT1
- Types
  - LQT1 syndrome: KVLQT voltage-gated K^+ **channel** (KCNA8; KCNQ1)
    - KCNQ1 ;Chromosome 11p15.5 ; Dominant or Recessive
      - Disease syndromes
        - Jervell & Lange-Nielsen Syndrome : Recessive
          - Mutation suppresses dominant negative effect of truncated splice variant on full length isoform
          - Heterzygotes: Some cardiac K^+ current available for repolarization
        - Romano-Ward (LQT1) : Dominant
          - Dominant negative effect of truncated splice variant on full length isoform
          - No delayed rectifier K^+ current
      - Disease mechanisms
        - Mutants often cause dominant negative effect on wild type channels
        - K^+-selective outward (Repolarizing I_{ks}) current: Reduced
        - Prolongation of cardiac action potential: Produces predisposition to cardiac arrhythmias
      - Prevalence: 42% of LQT syndromes
      - Cardiac
        - Stress-induced: Syncope; Palpitations; Torsade de pointe
        - Frequency of cardiac events with mutation: 63%
        - Risk of death from cardiac event: 4%
      - Congenital hearing loss
      - Onset: Earliest of common LQT syndromes
        - Males: Before puberty
        - Female: After puberty; Persisting cumulative risk
        - Median age: 9 years
      - Drugs provoking events
        - Mefloquine
        - Disopyramide
        - Terfenadine
        - Cisapride
      - Rx: Opening K^+ channels (Nicorandil); β-blockers; Not mexilletine
  - LQT2: HERG K^+ **channel** (KCNH2; I_{Kr})
    - Chromosome 7q35-q36; Dominant-negative
      - **Channel** behavior: Inward rectifying

- Normal function may suppress arrhythmias
- Mutations: Several mechanisms of defect
  - Defect in biosynthetic processing
    - HERG **channel** retained in the endoplasmic reticulum
  - No functional channels produced
  - HERG current with altered gating properties
- Prevalence: 45% of LQT syndromes
- Onset: Median age 12 years
- Cardiac clinical events
  - Precipitated by loud noise
  - Syncope, Aborted cardiac arrest, Sudden death
  - Frequency of cardiac events with mutation: 46%
  - Risk of death from cardiac event: 4%
- Drugs provoking events
  - Clarithromycin
  - Quinidine
  - Sulfamethoxazole
  - Procainamide
  - Oxatomide
- ? Rx by increasing serum K^+

- LQT3 : Cardiac Na^+ **channel** - α subunit; SCN5A
  - Chromosome 3p21-p24; Dominant
    - Mechanisms
      - Increased Na^+ **channel** activity during plateau phase of the action potential
      - Leads to extra component of inward current: Prolongs repolarization
    - Prevalence: 8% of LQT syndromes
    - Onset: Median age 16 years
    - Cardiac clinical events
      - Events occur at rest or during sleep
      - Syncope, Aborted cardiac arrest, Sudden death
      - Frequency of cardiac events with mutation: 18%
      - Risk of death from cardiac event: 20%
      - Cardiac events less frequent but more likely lethal than LQT1 or LQT2
    - Drugs provoking events: Halofantrine
    - Rx: Mexilletine; ? by Na **channel** blockade
    - Mutations also produce: Idiopathic ventricular fibrillation (Brugada syndrome)
- LQT4 : Ankyrin-B (ANK2)
  - Chromosome 4q25-q27; Dominant
    - Haploinsufficiency
    - Disease mechanism: Defective targeting of **calcium**-handling proteins to transverse tubule membranes
      - Inositol 1,4,5-trisphosphate receptor
      - **Sodium-calcium** exchanger
      - **Sodium-potassium** ATPase (Na^+/K^+ ATPase)
    - Clinical
      - Sinus node dysfunction: Onset in utero
      - Bradycardia or Junctional escape rhythm
      - Episodes of atrial fibrillation
- LQT5 : KCNE1 (minK protein)
  - Chromosome 21q22.1-q22.2; Dominant
- LQT6 : minK related peptide 1
  - Chromosome 21q22.1; Dominant
- Long QT with congenital deafness (Jervell-Lange-Nielsen)

- Chromosome 21q22.1-q22.2; Recessive
  - K^+ Voltage gated **channel**, ISK-related subfamily, Member 1 (KCNE1)
  - Same phenotype as LQT1
- Chromosome 11p15.5; Recessive
  - KCNQ1 (KCNA8; KVLQT1)

- Long QT syndrome with syndactyly (Timothy syndrome)
  - CACNA1C; Chromosome 12p13.3; Dominant
- Long QT syndrome: Acquired
  - HERG K^+ **channel** blockade
  - 2° Antiarrhythmic medications: Class IA or III

Concepts in channelopathies

What are the properties of the mutations in the chloride **channel** gene (CLC1) that determine whether a syndrome is inherited in a dominant or recessive pattern?

The dominant or recessive nature of a mutation depends on the ability of the mutant chloride **channel** monomers to polymerize with normal **channel** monomers. *Dominant* mutations complex with normal monomers producing defective channels. For some mutations one abnormal monomer is sufficient to destroy the function of a tetramer complex (e.g. Pro480Leu). For other mutations (e.g. Gly230Glu) it requires two abnomal monomers to destroy the **channel** function of a tetramer. In either case, only a minority of tetramers remain functional and myotonia results. *Recessive* mutations do not complex with normal monomers. Normal monomers are then free to complex with other normal monomers. This produces enough functional tetramers in heterozygotes (50% of the usual amount) to preserve normal membrane excitablity and myotonia does not occur.

What are the properties of the mutations in the **sodium channel** gene (SCN4A) that determine whether a syndrome presents with myotonia, paramyotonia, or weakness?

Many mutations produce abnormal *inactivation* of the **sodium channel**. This results in increased **sodium** conductance and membrane depolarization. Mild depolarization is associated with increased membrane excitability and myotonia. Strong depolarization produces membrane inexcitability and weakness. Some mutations only reduce inactivation at low temperatures producing paramyotonic disorders (myotonia or weakness worse in the cold). Mutations in the inactivation gate (amino acid 1306) produce different degrees of disease severity depending on the size and charge of the side chain of the new amino acid. Alanine, with a short side chain produces mild myotonia fluctuans. Valine, with an intermediate side chain, produces paramyotonia congenita. Glutamic acid, with a long side chain and a negative charge, results in myotonia permanens.

CHANNEL TOXINS

Marine toxins
- Ciguatoxin
- Conotoxins
- Palytoxin (Clupeotoxism)
- Tetrodotoxin
- Shell fish
  - Saxitoxin: Paralytic
  - Domoic acid: Encephalopathic
  - Brevetoxins: Neurotoxic

Diarrheic
Other
Lidocaine
Potassium channel

Marine toxins: General[24]

- Clinical
  - Syndromes occur after ingestion of toxins
  - Systems involved
    - Gastrointestinal
    - Neurological: Peripheral nerves
  - Differs from painful cardiovascular effects of marine venom toxins
- Toxin properties
  - Heat and gastric-acid stable
  - Low molecular-weight
  - Affect voltage-gated Na+ channels: In myelinated & unmyelinated nerves

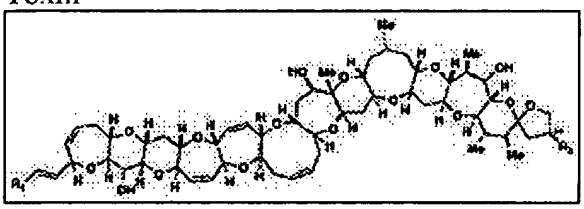
---

Ciguatera toxins[7,8,11]

Epidemiology
Toxicity
Clinical
Laboratory

- Epidemiology: Marine toxin
  - Geographic distribution
    - Caribbean
    - Indo-Pacific
    - Australia: Northeastern coast fish; Outbreaks in Sydney
  - Incidence
    - 10,000 to 50,000 annually
    - Most common illness 2° finfish consumption
    - Occurs in small clusters of patients who shared one, or a few, large fish
    - Some Pacific & Caribbean island nations up to 10% incidence
  - Patient characteristics
    - Males > Females
    - Age: 2nd & 3rd decade
    - Older individuals
      - Symptomatic first poisoning more common
      - Acute symptoms more severe
      - Duration of symptoms longer
  - Food chain
    - Microalgae contaminated with *Gamberdiscus*: Benthic dinoflagellate on dead coral
      - External link
    - Herbiverous fish consume contaminated microalgae
    - Carniverous fish eat contaminated herbivorous fish
    - Toxin is concentrated in all tissues of carnivorous fish: Especially liver & other viscera
    - Human ciguatera disease: Caused by ingestion of fish with high concentration of toxin
      - Toxic level: > 0.1 ppb (0.1 μg/kg)
      - Usually with ingestion of large fish: Rarely < 2 kg; Especially > 10 kg
      - Reef fish types

        - Barracuda (Sphyraena jello)
        - Ephanids: Flowery (Epinephelus fuscoguttatus) & spotted cod
        - Moray eel (Lycodotis): Most toxic
        - Serranids: Coral trout (*Plectropomus leopardus*) from Great Barrier reef; Grouper; Sea bass
        - Lutjanids: Red bass & snapper
        - Amberjack
        - Scombrids: Spanish mackerel (Scomberomorus commersom) & tunas
        - Carangids: Jacks & Scads
        - Lethrinids: Emperors & Scavengers
- Toxicity
    - Ingestion: Contaminated predatory fish
    - Toxin



        - Type: Lipophilic cyclic polyether
        - Properties
            - Heat-stable
            - Lipid soluble: Long retention in neuronal lipid membranes
        - Dinoflagellate toxins (*Gambierdiscus toxicus*)
            - Associated with dead coral & blue-green algae
            - > 20 different gambier- & ciguatoxins
                - Ciguatoxins bind to site 5 (transmembrane segment) on α-subunit of $Na^{\pm}$ **channel**
                - Most prolong Na^{+} **channel** opening
                - One blocks Na^{+} channels
            - Produced in precursor form by *Gamberdiscus toxicus*
            - Biotransformed to active more polar toxin in fish
            - Ciguatoxin types
                - Pacific: Pacific-ciguatoxin-1 (P-CTX-1); More toxic
                - Caribbean: Caribbean-ciguatoxin-1 (C-CTX-1)
        - Mechanisms of action
            - Inactivation of voltage-gated $Na^{\pm}$ channels
            - Increases nerve membrane excitability
            - P-CTX-1
                - TTX-sensitive Na^{+} channels open closer to normal resting membrane potential
                - TTX-resistant Na^{+} channels recover from inactivation more quickly
- Clinical
    - General
        - Gastrointestinal: More common in Caribbean; Earliest onset (~12 hours)
        - PNS: Indo-Pacific; Onset ~24 hours
        - CNS (Hallucinations): Indian Ocean
    - Rapid onset: 4 to 16 hours after ingestion
        - GI: Vomiting; Diarrhea; Abdominal pain
            - May produce electrolyte disturbances or dehydration: Especially children
            - Course: Self limiting over < 36 hours
        - Cardiac
            - Vasomotor: Bradycardia; Hypotension
        - Discomfort: Myalgias; Cramping; Pruritis; Headache
    - Longer term symptoms: Onset after 12 hours

- Most common: Weakness; Joint & Muscle pain; Paresthesias
- Sensory
  - Sensory loss
    - Temperature (80%)
    - Pin & Vibration (50%)
  - Paresthesias & Pruritis: Intense
    - Often presenting symptoms
    - Especially in extremities
    - Centrifugal spread from mouth & tongue
    - Duration: Days to Months
  - "Reversal" of hot & cold sensation
    - Cold objects produce uncomfortable burning
    - Warm: Fluids especially disturbing; Cold-sharp sensation
  - Feelings of loose teeth
  - Taste disturbance: Metallic
  - Pain: Limbs; Skin; Joints; Dental; Urethral
- Muscle
  - Pain
  - Weakness
    - May be related to neural involvement or inflammatory myopathy
    - Diffuse
    - Dysphagia
  - Fatigue
- Autonomic
  - Hypersalivation
  - Bradycardia
  - Laryngospasm
  - Hypotension
  - Pupils: Large or Small
- CNS
  - Headache: May be presenting feature
  - Depression
  - Cerebellar: Often later onset (Up to 10 days); Ataxia; Tremor
  - Short term memory loss
  - Insomnia
  - Coma in severe cases
- Death
  - Frequency
    - Mortality is region-specific: Up to 20% in occasional episodes
    - Pacific < 1% of patients
  - Due to: Shock; Respiratory failure
  - Occurs when more toxic parts of fish (liver, roe) ingested
- Recovery
  - Time course: 6 to 24 months
  - Most persistent symptoms: Pruritis; Arthralgia; Fatigue
  - ? Toxin stored in adipose tissue
  - Exacerbations with: Alcohol ingestion; Stress; Exercise; Weight loss

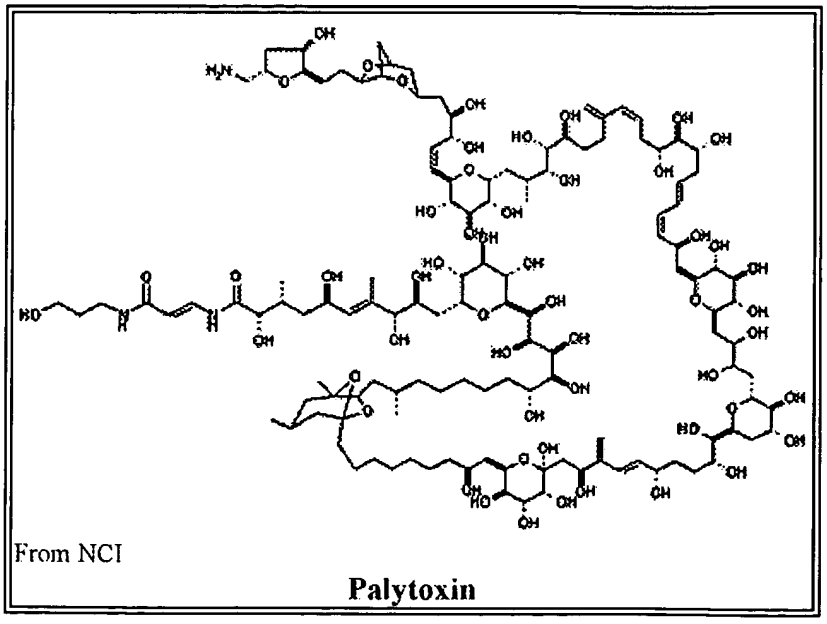
- Chronic syndrome
  - Frequency: 3% to 20% of severe intoxications
  - Fatigability
  - Weakness
  - Depression
  - Hypersomnolence
- Subsequent attacks

        - Often more severe than 1st attack
        - Patients more sensitive to low doses of toxin
        - Avoid eating fish for 6 months after initial attack
    - Pregnancy
        - ? Increased Fetal movements
        - Newborn after exposure: Normal or transient weakness
        - ? Breastfeeding may transmit toxin
    - Treatment
        - Symptomatic: Analgesics; Antihistamines
        - Mannitol
            - Not supported by controlled study
            - In 1st 48 hours; 1g/kg over 1/2 to 4 hours; May be repeated 1 or 2 times
- Laboratory
    - Electrophysiology
        - Slow NCV & F-waves
        - Prolonged refractory periods
        - Repetitive axonal firing
        - Mild cases
            - Normal routine electrophysiology
            - Latent tetany: Multiplets persisting > 2 min after cessation of hyperventilation or ischemia
    - Plasma cholinesterase: Reduced in 80%
    - Diagnostic testing
        - Mouse bioassay: Injection of fish extracts
        - Immunoassay for Pacific-ciguatoxin -1
        - Confirmation by liquid chromatography/tandem mass spectrometry
    - Pathology: Schwann cell cytoplasm edema
- Differential diagnosis
    - Clupeotoxism
    - Other marine toxin syndromes
        - Tetrodotoxin
        - Shell fish intoxication: Saxitoxin; Gonyautoxin
        - Scombroid: 2° Histamine accumulation in spoiled fish

---

Clupeotoxism

- Sources
    - Plankton-eating fish: Sardines & Herring (Clupeoid fish)
    - Hawaiian spear toxin
- Probable producing organism: *Ostreopsis siamensis* (Benthic dinoflagellate)
- Chemical class: Polyether
- Active agent: Palytoxin
    - Pore-forming toxin
    - Converts Na^+/K^+ pumps into nonselective cation channels
    - Increases H^+ influx into cells: Increases intracellular Ca^{++} in cardiac myocytes
    - Causes depolarization, Na^+ accumulation & Ca^{++} overload
    - Causes contraction of smooth & skeletal muscle



From NCI

Palytoxin

- May produce hemolysis
- Highly potent: Only botulinum & tetanus toxins active at lower concentrations

- Clinical
  - Produces a similar syndrome to ciguatera: May be mild or fatal
  - Pain & Cramps: Muscle & Back
  - Gastrointestinal: Nausea, Vomiting, Abdominal cramps & diarrhoea
  - Sensory
    - Metallic taste
    - Paresthesias
  - Weakness
  - Pupils: Dilated
  - CNS: Ataxia; Coma
  - Mortality rate: High
- Laboratory
  - CK high
  - Dark urine

Conotoxins

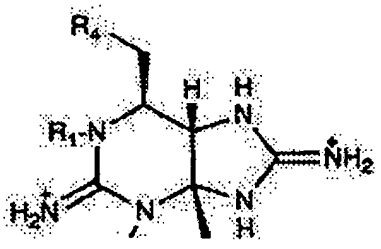
- α: Bind to AChRs
  - Muscle nicotinic: GI, GIA, GII, MI, SI, SIA, SII, EI
    - MI binds to α-γ subunit interface
    - EI binds to α-δ subunit interface > α-γ
  - Neuronal
    - MII binds to $\alpha_3\beta_2$
    - IMI binds to α_7
- δ: Bind to $Na^{\pm}$ channels
- μ: Bind to $Na^{\pm}$ channels
- ω: Bind to Ca^{++} channels
  - N-type: GVIA, MVIIA, SVIA
  - N-, P- & Q-type: MVIIC, MVIID

Lidocaine

- Blocks voltage-gated Na^+ channels
- Usage dependent
- Requires open Na^+ channels
- Dosage effects
  - Partial block: Slow NCV
  - Higher dosage: Conduction block
  - Very high dose: K^+ **channel** block also

Saxitoxin

- Toxicity
  - Associated with "Red tides"
  - Ingestion
    - Contaminated bivalve shellfish (mussels, oysters & clams)
    - Filter feeding of shell fish concentrates toxins



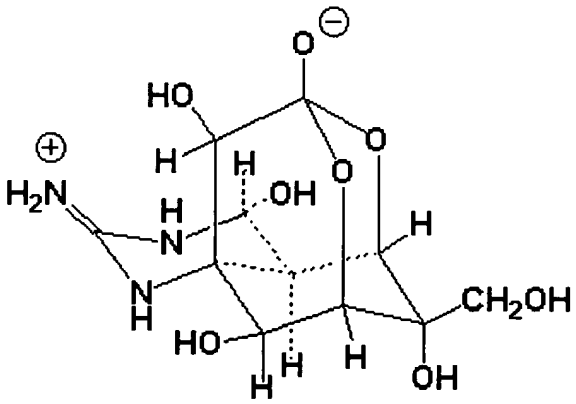
    - Origin of toxin: Dinoflagellates (*Gonyaulax* toxin)
        - *Alexandrium* spp
        - *Pyrodinium bahamense* var *compressum*
        - *Gymnodinium catenatum*
        - Xanthid crab
        - External link
    - Toxin type & properties
        - Guanidinium
        - Heterocyclic
        - Water soluble
        - Heat stable
    - Mechanism of action
        - Binds to site 1 on voltage gated Na^+ **channel** (Tetrodotoxin-sensitive **channel**)
        - Blocks Na^+ flux
- Clinical
    - Onset
        - Rapid: 1/2 to 3 hous after ingestion
        - More rapid with increased severity of intoxication
    - Paresthesias & Numbness
        - Early: Lips, tongue, extremities (distal)
        - May become generalized
    - Weakness: Extremities, bulbar, respiratory
    - Tendon reflexes: Preserved early
    - CNS: Coma; Most patients alert
    - Systemic: Cardiac arrhythmias
    - Other
        - Headache
        - Nausea & vomiting
        - Hypersalivation & Diaphoresis
    - Recovery: 2 to 7 days
    - Death: Usually in first 12 hours
    - External link: Epidemic report
- Laboratory
    - Electrophysiology
        - Slow NCV
        - Long distal latencies
        - Small motor & sensory action potentials
        - Conduction block
    - Pathology: No morphologic changes
- Diagnosis
    - Mouse bioassay
    - HPLC
- Differential diagnosis: Similar clinical syndromes
    - Tetrodotoxin
    - Crab poisoning: External link
- External link: Neil Edwards

Tetrodotoxin

- Toxicity
    - Ingestion: Improperly prepared fish
        - Species
            - Tetraodontiformes (Bony fish): Fugu rubripes (puffer) Sheroides rubripes (globe)

        - Other: Blue-ringed octopus bite
      - Concentrated in organs: Liver > Gonads (ovary) > Intestine > Skin
      - Usual patterns of ingestion
        - Served from October through March
        - Served with enough toxin: Causes tingling of lips
    - Toxin
      - Type: Guanidinium; Heterocyclic
      - Water soluble
      - Produced by bacteria (Alteromas), not directly by fish
    - Mechanism of action
      - Binds to site 1 on voltage gated Na^+ **channel**: Occludes outer pore
        - Neutralization of negative amino acids 942 & 945 of S5-S6 loop reduces binding
        - Puffer fish have Na^+ **channel** mutation: Reduced toxin binding to own channels
      - Blocks Na^+ flux
        - Guanidinium moiety enters **channel**
        - Action independent of whether **channel** is open or closed
      - Physiology
        - Reduced action potential generation
        - Reduced propagation of action potentials

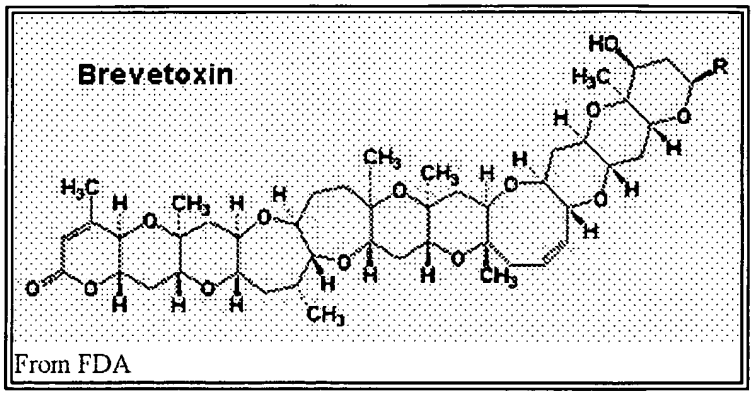
- Clinical
  - Onset
    - Rapid
    - 15 minutes to 12 hours after toxin ingestion
  - Sensory
    - Numbness & paresthesia
      - Lips, tongue, extremities
    - Loss: ? Reduced proprioception
  - Weakness
    - Extremities: Distal > Proximal
    - Bulbar & Facial
    - Respiratory
  - Tendon reflexes: Preserved early
  - CNS
    - Dizziness
    - Ataxia
    - Coma
  - Autonomic: With more severe intoxication
    - Cardiac rhythm: Arrhythmias; Bradycardia
    - Hypotension
    - Pupils: Fixed, Dilated
  - Consciousness: Normal
  - Recovery: 4 to 5 days
- Laboratory
  - Diagnosis: Toxin detection in urine
  - Electrophysiology
    - NCV: Slow
    - Long distal latencies
    - Conduction block
    - Small motor & sensory action potentials
    - High threshold for stimulation
  - Pathology: No morphologic changes
- Prognosis
  - Mortality: High (50%)



Tetrodotoxin

- Good after survival for 24 hours
- External link: Jim Johnson

Brevetoxins



From FDA

- Epidemiology: Human poisoning reported in
  - Florida: West coast
  - North Carolina
  - New Zealand
- Organism in shell fish: Marine dinoflagellate *Gymnodinium brevis*
- Chemistry
  - Lipid-soluble polyether toxins
  - Bind to voltage sensitive Na^+ channels
    - Bind at site 5 on Na^+ channels
    - Enhance Na^+ entry into cells
    - Neuroexcitatory effect: Cause nerve-cell depolarization & spontaneous firing
- Clinical
  - Gastrointestinal effects: Abdominal pain, Nausea & Diarrhea
  - Neurotoxic: Ciguatera-like
    - Paraesthesia
    - Temperature reversal
    - Myalgia
    - Vertigo
    - Ataxia
  - Other
    - Rectal-burning & pain
    - Headache
    - Bradycardia
    - Mydriasis
  - Severity: Usually mild
  - Treatment: Supportive care

Domoic Acid

- Epidemiology
  - One human outbreak: Canada 1987; Mussels
  - Mass deaths of marine mammals & sea birds
    - Pacific coast of Mexico, Washington & Oregon
- Biology
  - Ingestion of contaminated organisms
  - Produced by microscopic algae: *Nitzschia*
- Chemistry
  - Heat stable
  - Water soluble
  - Neuroexcitatory amino: Acts like glutamic acid
- Clinical: Amnesic syndrome
  - Gastrointestinal
    - Onset: 5 hours after exposure
    - Vomiting, abdominal cramps & diarrhea
    - More common in younger patients
  - Toxic encephalopathy: Severe memory loss & confusion

- Onset: 48 hours
- Headache
- Eye movements: Disordered
- CNS excitability: Seizures; Myoclonus
- Mental status disorders
    - Confusion & Disorientation
    - Short-term memory loss
    - Coma

- Systemic features
    - Hemodynamic instability
    - Cardiac arrhythmias
    - Respiratory secretions: Profuse
- Prognosis: Worse in older patients
- Pathology: Neuronal loss in amygdala and hippocampus

Diarrheic shellfish poisoning (DSP)

- Caused by group of high molecular weight polyethers
- Toxins
    - Okadaic acid
    - Dinophysis toxins
    - Pectenotoxins
    - Yessotoxin

Return to Myopathies
Return to Neuromuscular Syndromes
Return to Neuromuscular Home Page

References

1. TINS Supplement: June 1996
2. Toxin illustrations from Ion **Channel** Research
3. Neurology 1997;49:1196-1199br> 4. Curr Opin Neurobiol 1999;9:267-273
5. Trends in Neurosciences 1999;22:488-495
6. Am J Hum Genet 2000;66 (May)
7. Medical Journal of Australia 2000;172:176-179
8. Medical Journal of Australia 2000;172:160-162
9. Physiol Rev 2000;79:1317-1372; Clin Neurophysiol 2001;112:2-18
10. TINS 2000;23:393-398, Arch Neurol 2003;60:496-500
11. Muscle Nerve 2000;23:1598-1603; JNNP 2001;70:4-8
12. Nature Reviews:Neuroscience 2001;2:387-396
13. Arch Neurol 2001;58:1649-1653
14. Physiol Rev 2002;82:503-568
15. Nature 2002;417;501-502
16. Ann Intern Med 2002;137:981-992
17. Nature Neuroscience 2003;6;468-475
18. Physiological Reviews 2003;83:117-161
19. Ann Neurol 2003;54:239-243
20. Nature 2004;430:232-235
21. Hum Mol Genet 2004;13:1703+ 1714
22. Molec Neurobiol 2004;30:279-305
23. Molec Neurobiol 2004;30:341-357

24. Lancet Neurology 2005;4:219-228
25. Current Pharmaceutical Design 2005;11:1915-1940

7/23/2006